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(54) Title: METHODS OF TREATING RESPIRATORY DISEASE USING ANTAGONISTS OF INTERLEUKIN-1 RECEPTOR TYPE 1

(57) Abstract: Disclosed is the use of an antagonist of Interleukin 1 receptor type 1 (IL-1R1) for the manufacture of a medicament treating, preventing or suppressing lung inflammation or a respiratory disease. In some embodiments of the described invention, the medicament is for local administration to pulmonary tissue. Also disclosed are methods for treating lung inflammation or a respiratory disease.



WO 2006/059108 A2

METHODS OF TREATING RESPIRATORY DISEASE USING ANTAGONISTS OF INTERLEUKIN-1 RECEPTOR TYPE 1

RELATED APPLICATIONS

This application is a continuation-in-part of International Application No. PCT/GB2005/002163, which designated the United States and was filed on May 31, 2005, which claims the benefit of U.S. Provisional Application No. 60/632,361, filed on December 2, 2004; and this application claims priority under 35 U.S.C. § 119 or 365 to United Kingdom, Application No. 0521621.3, filed October 24, 2005. The entire teachings of the above applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The *in vivo* use of many agents with therapeutic or diagnostic potential is not possible. Larger agents that have *in vivo* serum half-lives that are sufficiently long to allow for therapeutic or diagnostic efficacy often are unable to penetrate tissues or organs to produce a desired therapeutic or diagnostic effect at a desired location. Smaller agents are able to enter tissues and organs, but frequently have short *in vivo* serum half-lives, and are rapidly cleared from the systemic circulation. For example, the *in vivo* serum half-life of dAb monomers is about 30 minutes. (See, Examples 9 and 13 of WO 2004/081026 A2.) Similarly, the *in vivo* serum half-life of antigen-binding fragments of antibodies, particularly Fv fragments, is also short and makes them unsuitable for many *in vivo* therapeutic and diagnostic applications. (Peters *et al.*, *Science* 286(5439):434 (1999).) Further, altering or modifying such agents to increase the *in vivo* serum half-life can reduce the activity of the agent.

Certain agents that bind Interleukin 1 Receptor Type 1 (IL-1R1) and neutralize its activity have proven to be effective therapeutic agents for certain inflammatory conditions, such as moderately to severely active rheumatoid arthritis. However, other agents that bind IL-1R1, such as the anti-IL-1R1 antibody AMG 108 (Amgen) have failed to meet primary endpoints in clinical studies. No agents that

bind and antagonize IL-1R1 have been demonstrated to be effective in treating lung inflammation or respiratory diseases, such as chronic obstructive pulmonary disease (COPD).

5 A need exists for improved agents that antagonize IL-1R1 and method for administering such agents to treat lung inflammation and lung disease.

SUMMARY OF THE INVENTION

The invention relates to use of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1) for the manufacture of a medicament for treating a respiratory disease, and to method of treating a respiratory disease that comprise administering an
10 antagonists of IL-1R1. The respiratory disease can be, for example, selected from the group consisting of lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary
15 thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic
20 pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary
25 tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, sarcoidosis, and Wegener's granulomatosis.

The medicament can be for systemic or local administration. In some embodiments, the medicament is for intraperitoneal or subcutaneous administration. In other embodiments, the medicament is for local administration to pulmonary
30 tissue, for example, the medicament can be for inhalation or intranasal administration.

In some embodiments the medicament further comprises antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1, p55), or is for administration together with an antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1, p55).

In one aspect, the method relates to use of an antagonist of IL-1R1 for
5 manufacture of a medicament for treating a respiratory. In some embodiments, the antagonist of IL-1R1 comprises a polypeptide domain that has binding specificity for Interleukin-1 Receptor Type 1 (IL-1R1) and inhibits binding of a ligand selected from the group consisting of Interleukin-1 α (IL-1 α) and Interleukin-1 β (IL-1 β) to IL-1R1. For example, the polypeptide domain that has binding specificity for IL-
10 1R1 can be selected from the group consisting of an antibody or antigen-binding fragment thereof, Interleukin-1 receptor antagonist (IL-1ra) or a functional variant of IL-1ra.

Preferably, the polypeptide domain that has binding specificity for IL-1R1 inhibits binding of said ligand to IL-1R1 with an IC₅₀ that is ≤ 1 μ M.
15 In some embodiments, the polypeptide domain that has binding specificity for IL-1R1 inhibits IL-1 α - or IL-1 β -induced release of Interleukin-8 by MRC-5 cells (ATCC Accession No. CCL-171) in an *in vitro* assay with a ND₅₀ that is ≤ 1 μ M, or preferably ≤ 1 nM. In other embodiments, the polypeptide domain that has binding specificity for IL-1R1 inhibits IL-1 α - or IL-1 β -induced release of Interleukin-6 in a
20 whole blood assay with a ND₅₀ that is ≤ 1 μ M.

In particular embodiments, the polypeptide domain that has binding specificity for IL-1R1 is an antigen-binding fragment of an antibody, and said antigen-binding fragment is an immunoglobulin single variable domain. Preferably, one or more of the framework regions (FR) in said immunoglobulin single variable
25 domain comprise (a) the amino acid sequence of a human framework region, (b) at least 8 contiguous amino acids of the amino acid sequence of a human framework region, or (c) an amino acid sequence encoded by a human germline antibody gene segment, wherein said framework regions are as defined by Kabat. The amino acid sequences of one or more framework regions in said immunoglobulin single variable
30 domain can be the same as the amino acid sequence of a corresponding framework region encoded by a human germline antibody gene segment, or the amino acid sequences of one or more of said framework regions can collectively comprise up to

5 amino acid differences relative to the corresponding framework regions encoded by a human germline antibody gene segment. In some embodiments, the amino acid sequences of FR1, FR2, FR3 and FR4 in the immunoglobulin single variable domain are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment, or the amino acid sequences of FR1, FR2, FR3 and FR4 collectively contain up to 10 amino acid differences relative to the corresponding framework regions encoded by a human germline antibody gene segment. In particular embodiments, the immunoglobulin single variable domain comprises FR1, FR2 and FR3 regions, and the amino acid sequence of said FR1, FR2 and FR3 are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment. In more particular embodiments, the human germline antibody gene segment comprises is DPK9 and JK1.

The antagonist of IL-1R1 can comprise an immunoglobulin single variable domain that competes for binding to IL-1R1 with a dAb selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID

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30 130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID
NO:348), and DOM4-133 (SEQ ID NO:349).

In particular embodiments, the antagonist of IL-1R1 comprises an immunoglobulin single variable domain immunoglobulin single variable domain comprises an amino acid sequence that has at least about 90% amino acid sequence identity with an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78),

DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113 (SEQ ID NO:86), DOM4-114 (SEQ ID NO:87), DOM4-115 (SEQ ID NO:88), DOM4-116 (SEQ ID NO:89), DOM4-117 (SEQ ID NO:90), DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102), DOM4-122-8 (SEQ ID NO:103), DOM4-122-9 (SEQ ID NO:104), DOM4-122-10 (SEQ ID NO:105), DOM4-122-11 (SEQ ID NO:106), DOM4-122-12 (SEQ ID NO:107), DOM4-122-13 (SEQ ID NO:108), DOM4-122-14 (SEQ ID NO:109), DOM4-122-15 (SEQ ID NO:110), DOM4-122-16 (SEQ ID NO:111), DOM4-122-17 (SEQ ID NO:112), DOM4-122-18 (SEQ ID NO:113), DOM4-122-19 (SEQ ID NO:114), DOM4-122-20 (SEQ ID NO:115), DOM4-122-21 (SEQ ID NO:116), DOM4-122-22 (SEQ ID NO:117), DOM4-122-25 (SEQ ID NO:118), DOM4-122-26 (SEQ ID NO:119), DOM4-122-27 (SEQ ID NO:120), DOM4-122-28 (SEQ ID NO:121), DOM4-122-29 (SEQ ID NO:122), DOM4-122-30 (SEQ ID NO:123), DOM4-122-31 (SEQ ID NO:124), DOM4-122-32 (SEQ ID NO:125), DOM4-122-33 (SEQ ID NO:126), DOM4-122-34 (SEQ ID NO:127), DOM4-122-35 (SEQ ID NO:128), DOM4-122-36 (SEQ ID NO:129), DOM4-122-37 (SEQ ID NO:130), DOM4-122-38 (SEQ ID NO:131), DOM4-122-39 (SEQ ID NO:132), DOM4-122-40 (SEQ ID NO:133), DOM4-122-41 (SEQ ID NO:134), DOM4-122-42 (SEQ ID NO:135), DOM4-122-43 (SEQ ID NO:136), DOM4-122-44 (SEQ ID NO:137), DOM4-122-45 (SEQ ID NO:138), DOM4-122-46 (SEQ ID NO:139), DOM4-122-47 (SEQ ID NO:140), DOM4-122-48 (SEQ ID NO:141), DOM4-122-49 (SEQ ID NO:142), DOM4-122-50 (SEQ ID NO:143), DOM4-122-51 (SEQ ID NO:144), DOM4-122-52 (SEQ ID NO:145), DOM4-122-54 (SEQ ID NO:146), DOM4-122-55 (SEQ ID NO:147), DOM4-122-56 (SEQ ID NO:148), DOM4-122-57 (SEQ ID NO:149), DOM4-122-58 (SEQ ID NO:150), DOM4-122-59 (SEQ ID NO:151), DOM4-122-60 (SEQ ID NO:152), DOM4-122-61 (SEQ ID NO:153), DOM4-122-62 (SEQ ID NO:154), DOM4-122-63 (SEQ ID NO:155),

DOM4-122-64 (SEQ ID NO:156), DOM4-122-65 (SEQ ID NO:157), DOM4-122-66 (SEQ ID NO:158), DOM4-122-67 (SEQ ID NO:159), DOM4-122-68 (SEQ ID NO:160), DOM4-122-69 (SEQ ID NO:161), DOM4-122-70 (SEQ ID NO:162), DOM4-122-71 (SEQ ID NO:163), DOM4-122-72 (SEQ ID NO:164), DOM4-122-73 (SEQ ID NO:165), DOM4-123 (SEQ ID NO:166), DOM4-124 (SEQ ID NO:167) DOM4-125 (SEQ ID NO:168), DOM4-126 (SEQ ID NO:169), DOM4-127 (SEQ ID NO:170), DOM4-128 (SEQ ID NO:171), DOM4-129 (SEQ ID NO:172), DOM4-129-1 (SEQ ID NO:173,) DOM4-129-2 (SEQ ID NO:174), DOM4-129-3 (SEQ ID NO:175), DOM4-129-4 (SEQ ID NO:176), DOM4-129-5 (SEQ ID NO:177), DOM4-129-6 (SEQ ID NO:178), DOM4-129-7 (SEQ ID NO:179), DOM4-129-8 (SEQ ID NO:180), DOM4-129-9 (SEQ ID NO:181), DOM4-129-10 (SEQ ID NO:182), DOM4-129-11 (SEQ ID NO:183), DOM4-129-12 (SEQ ID NO:184), DOM4-129-13 (SEQ ID NO:185), DOM4-129-14 (SEQ ID NO:186), DOM4-129-15 (SEQ ID NO:187), DOM4-129-16 (SEQ ID NO:188), DOM4-129-17 (SEQ ID NO:189), DOM4-129-18 (SEQ ID NO:190), DOM4-129-19 (SEQ ID NO:191), DOM4-129-20 (SEQ ID NO:192), DOM4-129-21 (SEQ ID NO:193), DOM4-129-22 (SEQ ID NO:194), DOM4-129-23 (SEQ ID NO:195), DOM4-129-24 (SEQ ID NO:196), DOM4-129-25 (SEQ ID NO:197), DOM4-129-26 (SEQ ID NO:198), DOM4-129-27 (SEQ ID NO:199), DOM4-129-28 (SEQ ID NO:200), DOM4-129-29 (SEQ ID NO:201), DOM4-129-31 (SEQ ID NO:202), DOM4-129-32 (SEQ ID NO:203), DOM4-129-33 (SEQ ID NO:204), DOM4-129-34 (SEQ ID NO:205), DOM4-129-35 (SEQ ID NO:206), DOM4-129-37 (SEQ ID NO:207), DOM4-129-38 (SEQ ID NO:208), DOM4-129-39 (SEQ ID NO:209), DOM4-129-40 (SEQ ID NO:210), DOM4-129-41 (SEQ ID NO:211), DOM4-129-42 (SEQ ID NO:212), DOM4-129-43 (SEQ ID NO:213), DOM4-129-44 (SEQ ID NO:214), DOM4-130 (SEQ ID NO:215), DOM4-130-1 (SEQ ID NO:216), DOM4-130-2 (SEQ ID NO:217), DOM4-130-3 (SEQ ID NO:218), DOM4-130-4 (SEQ ID NO:219), DOM4-130-5 (SEQ ID NO:220), DOM4-130-6 (SEQ ID NO:221), DOM4-130-7 (SEQ ID NO:222), DOM4-130-8 (SEQ ID NO:223), DOM4-130-9 (SEQ ID NO:224), DOM4-130-10 (SEQ ID NO:225), DOM4-130-11 (SEQ ID NO:226), DOM4-130-12 (SEQ ID NO:227), DOM4-130-13 (SEQ ID NO:228), DOM4-130-14 (SEQ ID NO:229), DOM4-130-15 (SEQ ID NO:230), DOM4-130-

16 (SEQ ID NO:231), DOM4-130-17 (SEQ ID NO:232), DOM4-130-18 (SEQ ID NO:233), DOM4-130-19 (SEQ ID NO:234), DOM4-130-20 (SEQ ID NO:235), DOM4-130-21 (SEQ ID NO:236), DOM4-130-22 (SEQ ID NO:237), DOM4-130-23 (SEQ ID NO:238), DOM4-130-24 (SEQ ID NO:239), DOM4-130-25 (SEQ ID NO:240), DOM4-130-26 (SEQ ID NO:241), DOM4-130-27 (SEQ ID NO:242), DOM4-130-28 (SEQ ID NO:243), DOM4-130-31 (SEQ ID NO:244), DOM4-130-32 (SEQ ID NO:245), DOM4-130-33 (SEQ ID NO:246), DOM4-130-34 (SEQ ID NO:247), DOM4-130-35 (SEQ ID NO:248), DOM4-130-36 (SEQ ID NO:249), DOM4-130-37 (SEQ ID NO:250), DOM4-130-38 (SEQ ID NO:251), DOM4-130-39 (SEQ ID NO:252), DOM4-130-40 (SEQ ID NO:253), DOM4-130-41 (SEQ ID NO:254), DOM4-130-42 (SEQ ID NO:255), DOM4-130-43 (SEQ ID NO:256), DOM4-130-44 (SEQ ID NO:257), DOM4-130-45 (SEQ ID NO:258), DOM4-130-46 (SEQ ID NO:259), DOM4-130-47 (SEQ ID NO:260), DOM4-130-48 (SEQ ID NO:261), DOM4-130-49 (SEQ ID NO:262), DOM4-130-50 (SEQ ID NO:263), DOM4-130-51 (SEQ ID NO:264), DOM4-130-52 (SEQ ID NO:265), DOM4-130-53 (SEQ ID NO:266), DOM4-130-54 (SEQ ID NO:267), DOM4-130-55 (SEQ ID NO:268), DOM4-130-56 (SEQ ID NO:269), DOM4-130-57 (SEQ ID NO:270), DOM4-130-58 (SEQ ID NO:271), DOM4-130-59 (SEQ ID NO:272), DOM4-130-60 (SEQ ID NO:273), DOM4-130-61 (SEQ ID NO:274), DOM4-130-62 (SEQ ID NO:275), DOM4-130-63 (SEQ ID NO:276), DOM4-130-64 (SEQ ID NO:277), DOM4-130-65 (SEQ ID NO:278), DOM4-130-66 (SEQ ID NO:279), DOM4-130-67 (SEQ ID NO:280), DOM4-130-68 (SEQ ID NO:281), DOM4-130-69 (SEQ ID NO:282), DOM4-130-70 (SEQ ID NO:283), DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287), DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID NO:292), DOM4-130-80 (SEQ ID NO:293), DOM4-130-81 (SEQ ID NO:294), DOM4-130-82 (SEQ ID NO:295), DOM4-130-83 (SEQ ID NO:296), DOM4-130-84 (SEQ ID NO:297), DOM4-130-85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID NO:300), DOM4-130-88 (SEQ ID NO:301), DOM4-130-89 (SEQ ID NO:302), DOM4-130-90 (SEQ ID NO:303), DOM4-130-91 (SEQ ID NO:304), DOM4-130-92 (SEQ ID NO:305),

DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID NO:307), DOM4-130-95 (SEQ ID NO:308), DOM4-130-96 (SEQ ID NO:309), DOM4-130-97 (SEQ ID NO:310), DOM4-130-98 (SEQ ID NO:311), DOM4-130-99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315), DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107 (SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324), DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

Preferrably, the antagonist of IL-1R1 comprises a polypeptide domain that has binding specificity for IL-1R1 binds human IL-1R1 with an affinity (KD) of about 300 nM to about 5 pM, as determined by surface plasmon resonance.

In some embodiments, the antagonist of IL-1R1 further comprises a half-life extending moiety. The half-life extending moiety can be, for example, a polyalkylene glycol moiety, serum albumin or a fragment thereof, transferrin receptor or a transferrin-binding portion thereof, or an antibody or antibody fragment comprising a binding site for a polypeptide that enhances half-life *in vivo*. In some embodiments, the half-life extending moiety is a polyethylene glycol moiety.

In other embodiments, the half-life extending moiety is an antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc

receptor. For example, the half-life extending moiety can be an immunoglobulin single variable domain that binds serum albumin or neonatal Fc receptor.

In particular embodiments, the half-life extending moiety is an immunoglobulin single variable domain that competes with a dAb selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784), for binding to human serum albumin.

In other embodiments, the half-life extending moiety is an immunoglobulin single variable domain that binds human serum albumin and comprises an amino acid sequence selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID

NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784).

If desired, the antagonist of IL-1R1 further comprises a polypeptide binding domain that has binding specificity for Tumor Necrosis Factor Receptor 1 (TNFR1, p55) and inhibits binding of Tumor Necrosis Factor Alpha (TNF α) to TNFR1.

Preferably, the antagonist of IL-1R1 binds human IL-1R1 with an affinity (KD) of about 300 nM to about 5 pM, as determined by surface plasmon resonance.

In more particular aspects, the invention relates to the use of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1) for the manufacture of a medicament for treating a respiratory disease, wherein said antagonist of IL-1R1 is a fusion protein or a conjugate comprising an antagonist of IL-1R1 moiety and a half-life extending moiety, wherein said antagonist of IL-1R1 moiety binds human IL-1R1 and inhibits

binding of a ligand selected from the group consisting of Interleukin-1 α (IL-1 α) and Interleukin-1 β (IL-1 β) to human IL-1R1, and said half-life extending moiety is a polypeptide binding moiety that contains a binding site with binding specificity for a polypeptide that enhances serum half-life *in vivo*.

5 In some embodiments, the antagonist of IL-1R1 moiety is human Interleukin 1 receptor antagonist (IL-1ra) or a functional variant of human IL-1ra. In other embodiments, the antagonist of IL-1R1 moiety is an immunoglobulin single variable domain that competes for binding to IL-1R1 with an anti-IL-1R1 dAb disclosed herein, or the antagonist of IL-1R1 moiety is an immunoglobulin single variable
10 domain that comprises an amino acid sequence that has at least about 90% amino acid sequence identity with an amino acid sequence of a dAb disclosed herein.

The half-life extending moiety can be serum albumin or a fragment thereof, transferrin receptor or a transferrin-binding portion thereof, or an antibody or antibody fragment comprising a binding site for a polypeptide that enhances half-life
15 *in vivo*. In particular embodiments, the half-life extending moiety is an immunoglobulin single variable domain that binds serum albumin and competes with an anti-serum albumin dAb disclosed herein for binding to serum albumin.

In other embodiments, the half-life extending moiety is an immunoglobulin single variable domain that binds human serum albumin comprises the amino acid
20 sequence of an anti-serum albumin dAb disclosed herein.

In more particular aspects, the invention relates to use of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1) for the manufacture of a medicament for treating a respiratory disease, wherein said antagonist of IL-1R1 comprises an immunoglobulin single variable domain that has binding specificity for human IL-
25 1R1 and inhibits binding of a ligand selected from the group consisting of Interleukin-1 α (IL-1 α) and Interleukin-1 β (IL-1 β) to human IL-1R1, and a polyethylene glycol moiety. In one embodiment, the immunoglobulin single variable domain competes for binding to human IL-1R1 with an anti-IL-1R1 dAb disclosed herein. In another embodiment, the immunoglobulin single variable
30 domain binds human serum albumin and comprises the amino acid sequence of an anti-serum albumin dAb disclosed herein.

The invention also relates to a pharmaceutical composition comprising an antagonist of IL-1R1 as described herein and a physiologically acceptable vehicle or carrier. In some embodiment, the pharmaceutical composition comprises a physiologically acceptable vehicle or carrier for parenteral administration (e.g.,
5 intravenous administration, subcutaneous administration). In other embodiment, the pharmaceutical composition comprises a physiologically acceptable vehicle or carrier for local administration (e.g., local administration to pulmonary tissue, such as by inhalation or intra-nasal administration. I

The invention also relates to a drug delivery device comprising a
10 pharmaceutical composition of the invention. For example, the drug deliver device can be a parenteral delivery device, intravenous delivery device, intramuscular delivery device, intraperitoneal delivery device, transdermal delivery device, pulmonary delivery device, intraarterial delivery device, intrathecal delivery device, intraarticular delivery device, subcutaneous delivery device, intranasal delivery
15 device, vaginal delivery device, and rectal delivery device. In particular embodiments the drug delivery device is selected from the group consisting of a syringe, a transdermal delivery device, a capsule, a tablet, a nebulizer, an inhaler, an atomizer, an aerosolizer, a mister, a dry powder inhaler, a metered dose inhaler, a metered dose sprayer, a metered dose mister, a metered dose atomizer, and a
20 catheter.

The invention also relates to a method for treating a respiratory disease comprising administering to a subject in need thereof an effective amount of an antagonist of IL-1R1 as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

25 FIGS. 1A and 1B are graphs showing the results of *in vitro* assays in which dAbs were tested for the ability to inhibit IL-1-induced IL-8 release from cultured MRC-5 cells (ATCC catalogue no. CCL-171). FIG. 1A shows a typical dose-response curve for an anti-IL-1R1 dAb referred to as DOM4-130 in such a cell assay. The ND₅₀ of DOM4-130 in the assay was approximately 500 - 1000 nM.
30 FIG. 1B shows a dose-response curve for anti-IL-1R1 dAbs referred to as DOM4-122 and DOM4-129 in such a cell assay. The ND₅₀ values of both dAbs was about 1 μ M.

FIGS. 2A and 2B are graphs showing the results of *in vitro* assays in which dAbs that underwent affinity maturation were tested for the ability to inhibit IL-1-induced IL-8 release from cultured MRC-5 cells (ATCC catalogue no. CCL-171). FIG. 2A shows a dose-response curve for DOM4-130-3, which is an affinity
5 matured variant of DOM4-130. The ND₅₀ for DOM4-130-3 in the assay was about 30 nM, compared to the ND₅₀ for DOM4-130 which was 500 - 1000 nM (see FIG. 1A). FIG 2B shows a dose-response curve for DOM4-130-46 and DOM4-130-51, which are affinity matured variants of DOM4-130, and for interleukin 1 receptor antagonist (IL-1ra). The ND₅₀ for DOM4-130-46 was about 1 nM in the assay, and
10 the ND₅₀ for DOM4-130-51 about 300 pM).

FIG. 3 is a graph showing the results of *in vitro* assays in which dAbs that underwent affinity maturation were tested for the ability to inhibit IL-1-induced IL-8 release from cultured MRC-5 cells (ATCC catalogue no. CCL-171). FIG. 3 shows a dose-response curve for DOM4-122-6, DOM4-129-1, DOM4-122-23, and IL-1ra.
15 DOM4-122-6 and DOM4-122-23 are affinity matured variants of DOM4-122, and DOM4-129-1 is an affinity matured variant of DOM4-129. Both DOM4-122-6 and DOM4-129-1 had an ND₅₀ of about 10 nM in the assay, and DOM4-122-23 had an ND₅₀ of approximately 1 nM in the assay.

FIG. 4 is a graph showing the results of an *in vitro* assay in which dAbs were
20 tested for the ability to inhibit IL-1-induced IL-6 release in human whole blood. The results show that an IL-1R1 control antibody (a-IL-1 RI Ab igG1), anti-IL-1R1 dAb (DOM4-130-54) and a dual specific format that contained an anti-IL-1R1 dAb and an anti-serum albumin dAb (DOM4-130-54/7h-8) each inhibited release of IL-6 in the assay, but that a dAb that binds serum albumin (DOM7h-8) did not.

25 FIG. 5 is a plot showing that an antagonist of IL-1R1 (IL1ra, a fusion protein in which IL-1ra was fused to an immunoglobulin single variable domain that binds mouse serum albumin) was efficacious in a subchronic model of tobacco smoke-induced (TS) chronic obstructive pulmonary disease (COPD) in C57BL/6 mice when administered intraperitoneally (10 mg/kg i.p.). The plot also shows that
30 administration of IL-1R1 together with a dAb that binds TNFR1 was even more efficacious in a subchronic model of tobacco smoke-induced (TS) chronic obstructive pulmonary disease (COPD) in C57BL/6 mice when administered

intraperitoneally. The plot shows the total number of cells present in bronchoalveolar lavage (BAL) of mice at completion of the study described in Example 2. The individual data points for each mouse in the study and the group averages (means; horizontal lines) are shown. The results show that antagonist of IL-1R1 reduced the number of cells in BAL by 58% compared to the untreated group (Veh), and that coadministration of the antagonist of IL-1R1 and an antagonist of TNFR1 reduced the number of cells in BAL by 88%. In contrast administration of ENBREL® (etanercept; Immunex Corporation) resulted in an increased number of total cells in BAL, although the increase was not statistically significant. TS, tobacco smoke-induced; Veh, vehicle; ns, not statistically significant.

FIG. 6 is a graph showing the levels of an immunoglobulin single variable domain that binds hen egg lysozyme (HEL-4) in the BAL at several time points after administration of the single variable domain to mice by pulmonary delivery. The graph shows HEL-4 was delivered efficiently into the deep lung. A dose related effect was observed. At 2 hours after administration, a maximum level of 700 ug/ml was detected in the lung with the 30 mg/kg dosing. The levels in the BAL are high for a prolonged period of time and declined gradually. The graph indicates that there was a slow release of HEL-4 into the surrounding tissues.

FIG. 7 is a graph showing the levels of HEL-4 in the serum at several time points after administration of the single variable domain to mice by pulmonary delivery. The graph shows that HEL-4 serum levels were detected in the 3 mg/kg and the 30 mg/kg dose groups. The serum levels showed a similar pattern as the BAL levels. There appeared to be a maximum level 2 hours after administration, followed by a slow decline. At 2 hours after administration, maximum levels of 3.5 µg/ml were detected in the serum with the 30 mg/kg dosing.

FIG. 8 is a graph showing the levels of IL-1ra (KINARET® (anakinra; Amgen)) in the BAL, lung tissue and serum at several time points after administration to mice by pulmonary delivery. The level in BAL was maximum at 1 hour after administration and was ~ 11 µg/ml (~2.75 µg in 0.25 ml of BAL fluid). The levels in the BAL were high for a prolonged period of time and show a gradual decline over 24 hrs. (> 10-fold decline after 24 hrs). The levels in lung tissue was maximum at 1 hr and was ~ 3.3µg/ml. The levels in the lung were high for a

prolonged period of time and show a gradual decline over 24hrs. (> 10-fold decline after 24 hrs). The level in the serum at 1 hr was lower than in BAL or lung tissue (~260 ng/ml). At 5 hrs the levels in the serum was maximum (350 ng/ml). The levels in the serum show a slow decline and after 24hrs there is only a 5-fold decline in the levels.

FIG. 9A-9 illustrates the amino acid sequences of several human dAbs that bind human IL-1R1. In some of the sequences, the amino acids of CDR1, CDR2 and CDR3 are underlined.

FIG. 10A-10BBB illustrates the nucleotide sequences of nucleic acids that encode the human dAbs shown in FIG. 9A-9X. In some of the sequences, the nucleotides encoding CDR1, CDR2 and CDR3 are underlined.

FIG. 11A is an alignment of the amino acid sequences of three V_κs selected by binding to mouse serum albumin (MSA). The aligned amino acid sequences are from V_κs designated MSA16, which is also referred to as DOM7m-16 (SEQ ID NO:723), MSA 12, which is also referred to as DOM7m-12 (SEQ ID NO:724), and MSA 26, which is also referred to as DOM7m-26 (SEQ ID NO:725).

FIG. 11B is an alignment of the amino acid sequences of six V_κs selected by binding to rat serum albumin (RSA). The aligned amino acid sequences are from V_κs designated DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), and DOM7r-8 (SEQ ID NO:731).

FIG. 11C is an alignment of the amino acid sequences of six V_κs selected by binding to human serum albumin (HSA). The aligned amino acid sequences are from V_κs designated DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), and DOM7h-7 (SEQ ID NO:737).

FIG. 11D is an alignment of the amino acid sequences of seven V_Hs selected by binding to human serum albumin and a consensus sequence (SEQ ID NO:738). The aligned sequences are from V_Hs designated DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), and DOM7h-27 (SEQ ID NO:745).

FIG. 11E is an alignment of the amino acid sequences of three V_κs selected by binding to human serum albumin and rat serum albumin. The aligned amino acid sequences are from V_κs designated DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), and DOM7r-14 (SEQ ID NO:748).

5 FIG. 12 is an illustration of the amino acid sequences of V_κs selected by binding to rat serum albumin (RSA). The illustrated sequences are from V_κs designated DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753).

10 FIG. 13A-13B is an illustration of the amino acid sequences of the amino acid sequences of V_Hs that bind rat serum albumin (RSA). The illustrated sequences are from V_Hs designated DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763),
15 DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), and DOM7r-33 (SEQ ID NO:767).

FIG. 14A is an illustration of the nucleotide sequence (SEQ ID NO:785) of a nucleic acid encoding human interleukin 1 receptor antagonist (IL-1ra) deposited in GenBank under accession number NM_173842. The nucleic acid has an open
20 reading frame starting at position 65.

FIG. 14B is an illustration of the amino acid sequence of human IL-1ra (SEQ ID NO:786) encoded by the nucleic acid shown in FIG. 15A (SEQ ID NO:785). The mature protein consists of 152 amino acid residues (amino acid residues 26-177 of SEQ ID NO:786).

25 FIG. 15 illustrates the amino acid sequences of several *Camelid* V_{HHS} that bind mouse serum albumin that are disclosed in WO 2004/041862. Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775),
30 Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence

N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), Sequence Q (SEQ ID NO:784).

DETAILED DESCRIPTION OF THE INVENTION

As used herein, “interleukin-1 receptor type 1” (IL-1R1; CD121a) refers to
5 naturally occurring or endogenous mammalian IL-1R1 proteins and to proteins
having an amino acid sequence which is the same as that of a naturally occurring or
endogenous corresponding mammalian IL-1R1 protein (*e.g.*, recombinant proteins,
synthetic proteins (*i.e.*, produced using the methods of synthetic organic chemistry)).
Accordingly, as defined herein, the term includes mature protein, polymorphic or
10 allelic variants, and other isoforms of a IL-1R1 (*e.g.*, produced by alternative
splicing or other cellular processes), and modified or unmodified forms of the
foregoing (*e.g.*, lipidated, glycosylated). Naturally occurring or endogenous IL-1R1
include wild type proteins such as mature IL-1R1, polymorphic or allelic variants
and other isoforms which occur naturally in mammals (*e.g.*, humans, non-human
15 primates). Such proteins can be recovered or isolated from a source which naturally
produces IL-1R1, for example. These proteins and IL-1R1 proteins having the same
amino acid sequence as a naturally occurring or endogenous corresponding IL-1R1,
are referred to by the name of the corresponding mammal. For example, where the
corresponding mammal is a human, the protein is designated as a human IL-1R1.

20 As used herein, “antagonist of interleukin-1 receptor type 1 (IL-1R1)
moiety” refers to any compound (*e.g.*, protein, polypeptide, peptide) that binds to IL-
1R1 and inhibiting a function of IL-1R1 (*e.g.*, inhibits binding of IL-1 α and/or IL-1 β
to IL-1R1, inhibits signaling through IL-1R1 upon binding of IL-1 α and/or IL-1 β).
An “antagonist of interleukin-1 receptor type 1” comprises an antagonists of
25 interleukin-1 receptor type 1 (IL-1R1) moiety, and can comprise additional moieties
if desired. An antagonist of interleukin-1 receptor type 1 (IL-1R1) moiety can be
formatted into a variety of suitable structures as described herein.

As used herein, “antagonist of interleukin-1 receptor type 1 (IL-1R1)” refers
to any compound (*e.g.*, polypeptide) that can be administered to an individual to
30 produce a beneficial therapeutic or diagnostic effect though binding to IL-1R1 and
inhibiting a function of IL-1R1 in the individual. Preferred “antagonists of IL-1R1”
comprise a peptide or polypeptide that binds IL-1R1 and inhibits a function of IL-

1R1, such as interleukin-1 receptor antagonist (IL-1ra) and functional variants thereof, and antibodies that bind IL-1R1 and antigen-binding fragments thereof (*e.g.*, dAbs). Antagonists of IL-1R1 include “conjugates,” such as a “covalent antagonist of IL-1R1 conjugate,” and a “noncovalent antagonists of IL-1R1 conjugate.”

- 5 Antagonists of IL-1R1 also include fusion proteins, such as, an “antagonist of IL-1R1 fusion proteins.”

The “conjugates” comprise an antagonist of IL-1R1 moiety (*e.g.*, IL-1ra or functional variant thereof, dAb) that is covalently or noncovalently bonded to a polypeptide binding moiety that contains a binding site (*e.g.*, an antigen-binding
10 site) with binding specificity for a polypeptide that enhances serum half-life *in vivo* (*e.g.*, serum albumin). The antagonist of IL-1R1 moiety can be covalently or noncovalently bonded to a polypeptide binding moiety that contains a binding site (*e.g.*, an antigen-binding site) that has binding specificity for a polypeptide that enhances serum half-life *in vivo*. The antagonist of IL-1R1 moiety can be covalently
15 or noncovalently bonded to the polypeptide binding moiety directly or indirectly (*e.g.*, through a suitable linker and/or noncovalent binding of complementary binding partners (*e.g.*, biotin and avidin)). When complementary binding partners are employed, one of the binding partners can be covalently bonded to the antagonist of IL-1R1 moiety directly or through a suitable linker moiety, and the
20 complementary binding partner can be covalently bonded to the polypeptide binding moiety directly or through a suitable linker moiety.

Preferably, the polypeptide binding moiety that has a binding site with binding specificity for a polypeptide that enhances serum half-live *in vivo* is an antigen-binding fragment of an antibody that binds serum albumin, (*e.g.*, a V_H, V_L,
25 V_{HH}). For example, the conjugate can be a “covalent antagonist of IL-1R1 conjugate” which refers to conjugates in which the antagonist of IL-1R1 moiety is covalently bonded to the antigen-binding fragment that binds serum albumin directly, or indirectly through a suitable linker moiety. The antagonist of IL-1R1 moiety can be bonded to the antigen-binding fragment at any suitable position, such
30 as the amino-terminus, the carboxyl-terminus or through suitable amino acid side chains (*e.g.*, the ϵ amino group of lysine). The antagonist of IL-1R1 can also be a “noncovalent antagonist of IL-1R1 conjugate,” which refers to conjugates in the

antagonist of IL-1R1 moiety and the antigen-binding fragment of an antibody that binds serum albumin are noncovalently bonded. The antagonist of IL-1R1 moiety can be noncovalently bonded to the antigen-binding fragment directly (*e.g.*, electrostatic interaction, hydrophobic interaction) or indirectly (*e.g.*, through
5 noncovalent binding of complementary binding partners (*e.g.*, biotin and avidin), wherein one partner is covalently bonded to the antagonist of IL-1R1 moiety and the complementary binding partner is covalently bonded to the antigen-binding fragment). When complementary binding partners are employed, one of the binding partners can be covalently bonded to the antagonist of IL-1R1 moiety directly or
10 through a suitable linker moiety, and the complementary binding partner can be covalently bonded to the antigen-binding fragment of an antibody that binds serum albumin directly or through a suitable linker moiety.

As used herein, “antagonist of IL-1R1 fusion” refers to a fusion protein that comprises an antagonist of interleukin-1 receptor type 1 (IL-1R1) moiety that is a
15 peptide or polypeptide, and an antigen-binding fragment of an antibody that binds serum albumin. The peptide or polypeptide antagonist of interleukin-1 receptor type 1 (IL-1R1) moiety, and the antigen-binding fragment of an antibody that binds serum albumin are present as discrete parts (moieties) of a single continuous polypeptide chain.

20 As used herein, “interleukin 1 receptor antagonist” (IL-1ra) refers to naturally occurring or endogenous mammalian IL-1ra proteins and to proteins having an amino acid sequence which is the same as that of a naturally occurring or endogenous corresponding mammalian IL-1ra protein (*e.g.*, recombinant proteins, synthetic proteins (*i.e.*, produced using the methods of synthetic organic chemistry)).
25 Accordingly, as defined herein, the term includes mature protein, polymorphic or allelic variants, and other isoforms of a IL-1ra (*e.g.*, produced by alternative splicing or other cellular processes), and modified or unmodified forms of the foregoing (*e.g.*, lipidated, glycosylated, PEGylated). Naturally occurring or endogenous IL-1ra include wild type proteins such as mature IL-1ra, polymorphic or allelic variants and
30 other isoforms which occur naturally in mammals (*e.g.*, humans, non-human primates). Such proteins can be recovered or isolated from a source which naturally produces IL-1ra, for example. These proteins and IL-1ra proteins having the same

amino acid sequence as a naturally occurring or endogenous corresponding IL-1ra, are referred to by the name of the corresponding mammal. For example, where the corresponding mammal is a human, the protein is designated as a human IL-1ra.

"Functional variants" of IL-1ra include functional fragments, functional
5 mutant proteins, and/or functional fusion proteins which can be produced using suitable methods (*e.g.*, mutagenesis (*e.g.*, chemical mutagenesis, radiation mutagenesis), recombinant DNA techniques). A "functional variant" antagonizes IL-1R1. Generally, fragments or portions of IL-1ra include those having a deletion and/or addition (*i.e.*, one or more amino acid deletions and/or additions) of an amino
10 acid (*i.e.*, one or more amino acids) relative to the mature IL-1ra (such as N-terminal, C-terminal or internal deletions). Fragments or portions in which only contiguous amino acids have been deleted or in which non-contiguous amino acids have been deleted relative to mature IL-1ra are also envisioned.

A functional variant of human IL-1ra can have at least about 80%, or at least
15 about 85%, or at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with the mature 152 amino acid form of human IL-1ra and antagonize human Interleukin-1 type 1 receptor. (See, Eisenberg *et al.*, *Nature* 343:341-346 (1990).) The variant can comprise one or more additional amino acids (*e.g.*,
20 comprise 153 or 154 or more amino acids). For example, the variant IL-1ra can have an amino acid sequence that consists of an amino-terminal methionine residue followed by residues 26 to 177 of SEQ ID NO:786. (KINERET® (anakinra), Amgen).

The phrase "immunoglobulin single variable domain" refers to an antibody
25 variable region (V_H , V_{HH} , V_L) that specifically binds an antigen or epitope independently of other V regions or domains; however, as the term is used herein, an immunoglobulin single variable domain can be present in a format (*e.g.*, homo- or hetero-multimer) with other variable regions or variable domains where the other regions or domains are not required for antigen binding by the single
30 immunoglobulin variable domain (*i.e.*, where the immunoglobulin single variable domain binds antigen independently of the additional variable domains).
"Immunoglobulin single variable domain" encompasses not only an isolated

antibody single variable domain polypeptide, but also larger polypeptides that comprise one or more monomers of an antibody single variable domain polypeptide sequence. A “domain antibody” or “dAb” is the same as an “immunoglobulin single variable domain” polypeptide as the term is used herein. An immunoglobulin single variable domain polypeptide, as used herein refers to a mammalian immunoglobulin single variable domain polypeptide, preferably human, but also includes rodent (for example, as disclosed in WO 00/29004, the contents of which are incorporated herein by reference in their entirety) or camelid V_{HH} dAbs. Camelid dAbs are immunoglobulin single variable domain polypeptides which are derived from species including camel, llama, alpaca, dromedary, and guanaco, and comprise heavy chain antibodies naturally devoid of light chain: V_{HH} . V_{HH} molecules are about ten times smaller than IgG molecules, and as single polypeptides, they are very stable, resisting extreme pH and temperature conditions.

“Complementary” Two immunoglobulin domains are “complementary” where they belong to families of structures which form cognate pairs or groups or are derived from such families and retain this feature. For example, a V_H domain and a V_L domain of an antibody are complementary; two V_H domains are not complementary, and two V_L domains are not complementary. Complementary domains may be found in other members of the immunoglobulin superfamily, such as the V_α and V_β (or γ and δ) domains of the T-cell receptor. Domains which are artificial, such as domains based on protein scaffolds which do not bind epitopes unless engineered to do so, are non-complementary. Likewise, two domains based on (for example) an immunoglobulin domain and a fibronectin domain are not complementary.

“Domain” A domain is a folded protein structure which retains its tertiary structure independently of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. By single antibody variable domain is meant a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example in which one or more loops have been

replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least in part the binding activity and specificity of the full-length domain.

5 “Repertoire” A collection of diverse variants, for example polypeptide variants which differ in their primary sequence. A library used in the present invention will encompass a repertoire of polypeptides comprising at least 1000 members.

 “Library” The term library refers to a mixture of heterogeneous
10 polypeptides or nucleic acids. The library is composed of members, each of which have a single polypeptide or nucleic acid sequence. To this extent, *library* is synonymous with *repertoire*. Sequence differences between library members are responsible for the diversity present in the library. The library may take the form of a simple mixture of polypeptides or nucleic acids, or may be in the form of
15 organisms or cells, for example bacteria, viruses, animal or plant cells and the like, transformed with a library of nucleic acids. Preferably, each individual organism or cell contains only one or a limited number of library members. Advantageously, the nucleic acids are incorporated into expression vectors, in order to allow expression of the polypeptides encoded by the nucleic acids. In a preferred aspect, therefore, a
20 library may take the form of a population of host organisms, each organism containing one or more copies of an expression vector containing a single member of the library in nucleic acid form which can be expressed to produce its corresponding polypeptide member. Thus, the population of host organisms has the potential to encode a large repertoire of genetically diverse polypeptide variants.

25 “Antibody” An antibody (for example IgG, IgM, IgA, IgD or IgE) or fragment (such as a Fab , F(ab')₂, Fv, disulphide linked Fv, scFv, closed conformation multispecific antibody, disulphide-linked scFv, diabody) whether derived from any species naturally producing an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas,
30 transfectomas, yeast or bacteria).

 “Dual-specific ligand” A ligand comprising a first immunoglobulin single variable domain and a second immunoglobulin single variable domain as herein

defined, wherein the variable regions are capable of binding to two different antigens or two epitopes on the same antigen which are not normally bound by a monospecific immunoglobulin. For example, the two epitopes may be on the same hapten, but are not the same epitope or sufficiently adjacent to be bound by a monospecific ligand. The dual specific ligands according to the invention are composed of variable domains which have different specificities, and do not contain mutually complementary variable domain pairs which have the same specificity. Dual-specific ligands and suitable methods for preparing dual-specific ligands are disclosed in WO 2004/058821, WO 2004/003019, and WO 03/002609, the entire teachings of each of these published international applications are incorporated herein by reference.

“Antigen” A molecule that is bound by a ligand according to the present invention. Typically, antigens are bound by antibody ligands and are capable of raising an antibody response *in vivo*. It may be a polypeptide, protein, nucleic acid or other molecule. Generally, the dual specific ligands according to the invention are selected for target specificity against a particular antigen. In the case of conventional antibodies and fragments thereof, the antibody binding site defined by the variable loops (L1, L2, L3 and H1, H2, H3) is capable of binding to the antigen.

“Epitope” A unit of structure conventionally bound by an immunoglobulin V_H/V_L pair. Epitopes define the minimum binding site for an antibody, and thus represent the target of specificity of an antibody. In the case of a single domain antibody, an epitope represents the unit of structure bound by a variable domain in isolation.

“Universal framework” A single antibody framework sequence corresponding to the regions of an antibody conserved in sequence as defined by Kabat (“Sequences of Proteins of Immunological Interest”, US Department of Health and Human Services) or corresponding to the human germline immunoglobulin repertoire or structure as defined by Chothia and Lesk, (1987) J. Mol. Biol. 196:910-917. The invention provides for the use of a single framework, or a set of such frameworks, which has been found to permit the derivation of virtually any binding specificity though variation in the hypervariable regions alone.

“Half-life” The time taken for the serum concentration of the ligand to reduce by 50%, *in vivo*, for example due to degradation of the ligand and/or clearance or sequestration of the ligand by natural mechanisms. The ligands of the invention are stabilised *in vivo* and their half-life increased by binding to molecules which resist degradation and/or clearance or sequestration. Typically, such molecules are naturally occurring proteins which themselves have a long half-life *in vivo*. The half-life of a ligand is increased if its functional activity persists, *in vivo*, for a longer period than a similar ligand which is not specific for the half-life increasing molecule. Thus, a ligand specific for HSA and a target molecule is compared with the same ligand wherein the specificity for HSA is not present, that it does not bind HSA but binds another molecule. For example, it may bind a second epitope on the target molecule. Typically, the half life is increased by 10%, 20%, 30%, 40%, 50% or more. Increases in the range of 2x, 3x, 4x, 5x, 10x, 20x, 30x, 40x, 50x or more of the half life are possible. Alternatively, or in addition, increases in the range of up to 30x, 40x, 50x, 60x, 70x, 80x, 90x, 100x, 150x of the half life are possible.

As used herein, the term “antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1)” refers to an agent (*e.g.*, a molecule, a compound) which binds TNFR1 and can inhibit a (*i.e.*, one or more) function of TNFR1. For example, an antagonist of TNFR1 can inhibit the binding of TNF α to TNFR1 and/or inhibit signal transduction mediated through TNFR1. Accordingly, TNFR1-mediated processes and cellular responses (*e.g.*, TNF α -induced cell death in a standard L929 cytotoxicity assay) can be inhibited with an antagonist of TNFR1. An antagonist of TNFR1 can be, for example, a small organic molecule, natural product, protein, peptide or peptidomimetic. Antagonists of TNFR1 can be identified, for example, by screening libraries or collections of molecules, such as, the Chemical Repository of the National Cancer Institute, as described herein or using other suitable methods. Preferred antagonists of TNFR1 are antibodies and antigen-binding fragments of antibodies (*e.g.*, dAb monomers).

30

The invention relates to use of an antagonist of IL-1R1 for the manufacture of a medicament preventing, treating, or mitigating lung inflammation or a

respiratory disease, such as those described herein (*e.g.*, chronic obstructive respiratory disease (COPD), asthma). Preferably, the medicament is for pulmonary delivery. The invention also relates to methods for preventing, treating, or mitigating lung inflammation or a respiratory disease comprising administering to a
5 subject in need thereof a therapeutically effective amount of antagonist of IL-1R1. Preferably, the method comprises administering the antagonist of IL-1R1 via pulmonary delivery. The invention also relates to pharmaceutical compositions for preventing, treating, or mitigating lung inflammation or a respiratory disease, such as those described herein (*e.g.*, chronic obstructive respiratory disease, asthma),
10 comprising as an active ingredient an antagonist of IL-1R1. Preferably, the pharmaceutical composition is for pulmonary delivery.

As described herein, polypeptide antagonists of IL-1R1 can be administered to a subject in need thereof to prevent, treat or mitigate lung inflammation, a respiratory disease or the symptoms thereof. For example, described herein are the
15 results of a study evaluating the efficacy of an antagonist of IL-1R1 (IL-1ra/anti-SA) in a mouse sub-chronic model of COPD induced by tobacco smoke. The results of this study revealed that the antagonists of IL-1R1 (IL-1ra/SA) was efficacious and significantly reduced the amount of inflammatory cells in lung of treated animals compared to control animals (reduced the number of total cells, macrophages,
20 polymorphic nuclear cells, lymphocytes and eosinophils recovered in bronchioalveolar lavage (BAL)). The results indicate the administration of other antagonists of IL-1R1, such as antagonists that comprise an immunoglobulin variable domain the binds IL-1R1 and inhibits binding of a ligand (*e.g.*, IL-1 α , IL-1 β) to IL-1R1, can also be administered to efficaciously treat lung inflammation, a
25 respiratory disease or the symptoms thereof.

Antagonists of IL-1R1, such as peptide and polypeptide antagonists, can be delivered to a subject in need thereof in therapeutically effective amounts by pulmonary delivery (*e.g.*, by inhalation). For example, as shown herein, pulmonary delivery of a dAb (HEL4) by inhalation resulted in efficient delivery of the dAb to
30 the deep lung, as assessed by the amount of dAb recovered in BAL collected up to 24 hours after the dAb was delivered. Accordingly, as shown by the studies described herein, respiratory diseases can be treated by administering an antagonist

of IL-1R1 locally to pulmonary tissue. This approach provides several advantages, such as minimizing or eliminating systemic side effects (*e.g.*, increased incidence of infection) that have been reported to be associated with systemic administration of agents that antagonize IL-1R1, such as KINERET (*e.g.*, anakinra, Amgen).

5

Antagonists of TNFR1 for Treating, Suppressing or Preventing Lung Inflammation and Respiratory Diseases.

The invention relates to methods for treating, suppressing or preventing lung inflammation and/or a respiratory disease comprising administering to a subject
10 (*e.g.*, a mammal, a human) in need thereof an effective amount of an antagonist of IL-1R1. The invention also relates to the use of an antagonist of IL-1R1 for the manufacture of a medicament for treating, suppressing or preventing lung inflammation and/or respiratory disease, and to a pharmaceutical composition for treating, suppressing or preventing lung inflammation and/or respiratory disease
15 comprising an antagonist of IL-1R1 as an active ingredient. Antagonists of TNFR1 suitable for use in the invention are described in detail herein and include small molecules, new chemical entities, IL-1ra and functional variants thereof, dAb monomers, and the like.

The invention comprises methods of administering antagonists of IL-1R1 for
20 in *in vivo* therapeutic and prophylactic applications, *in vivo* diagnostic applications and the like. Therapeutic and prophylactic uses of antagonists of IL-1R1 comprise administering an effective amount of antagonists of IL-1R1 to a recipient mammal or subject, such as a human.

For example, the antagonists of IL-1R1 will typically find use in preventing,
25 suppressing or treating lung inflammation and/or respiratory diseases, such as a condition in which lung inflammation is a symptom or part of the pathology, acute respiratory diseases, chronic respiratory diseases, acute inflammatory respiratory diseases and chronic inflammatory respiratory diseases. For example, the antagonists of IL-1R1 can be administered to treat, suppress or prevent lung
30 inflammation, chronic obstructive respiratory disease (*e.g.*, chronic bronchitis, chronic obstructive bronchitis, emphysema), asthma (*e.g.*, steroid resistant asthma), pneumonia (*e.g.*, bacterial pneumonia, such as Staphylococcal pneumonia),

hypersensitivity pneumonitis, pulmonary infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, 5 hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic pulmonary fibrosis, invasive pneumococcal disease (IPD), influenza, nontuberculous mycobacteria, pleural 10 effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary histiocytosis X (eosinophilic granuloma), pulmonary hypertension, pulmonary nocardiosis, pulmonary tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, 15 sarcoidosis, Wegener's granulomatosis, and non-small cell lung carcinoma.

In the instant application, the term "prevention" involves administration of the protective composition prior to the induction of the disease. "Suppression" refers to administration of the composition after an inductive event, but prior to the clinical appearance of the disease. "Treatment" involves administration of the protective 20 composition after disease symptoms become manifest.

Advantageously, dual- or multi-specific ligands may be used to target IL-1R1 and other molecules in therapeutic situations in the body of an organism. The invention therefore provides a method for synergising the activity of two or more binding domains (e.g., dAbs) wherein one domain binds IL-1R1 or other target in 25 pulmonary tissue, and the other domain binds a cytokine, receptor or other molecules, comprising administering a dual- or multi-specific ligand capable of binding to said two or more molecules (e.g., IL-1R1 and a cytokine). For example, this aspect of the invention relates to combinations of V_H domains and V_L domains, V_H domains only and V_L domains only.

30 Synergy in a therapeutic context may be achieved in a number of ways. For example, target combinations may be therapeutically active only if both targets are targeted by the ligand, whereas targeting one target alone is not therapeutically

effective. In another embodiment, one target alone may provide some therapeutic effect, but together with a second target the combination provides a synergistic increase in therapeutic effect (more than an additive effect).

Animal model systems which can be used to screen the effectiveness of the antagonists of IL-1R1 in preventing, suppressing or treating lung inflammation or a respiratory disease are available. For example, suitable animal models of respiratory disease include models of chronic obstructive respiratory disease (see, Groneberg, DA *et al.*, *Respiratory Research* 5:18 (2004)), and models of asthma (see, Coffman *et al.*, *J. Exp. Med.* 201(12):1875-1879 (2001)). Preferably, the antagonist of IL-1R1 is efficacious in a mouse tobacco smoke-induced model of chronic obstructive respiratory disease (e.g., the subchronic model disclosed herein) or a suitable primate model of asthma or chronic obstructive respiratory disease. More preferably, the antagonist of IL-1R1 is efficacious in a mouse tobacco smoke-induced model of chronic obstructive respiratory disease (e.g., the subchronic model disclosed herein) (See, also, Wright and Churg, *Chest*, 122:301-306 (2002)). For example, administering an effective amount of the ligand can reduce, delay or prevent onset of the symptoms of COPD in the model, as compared to a suitable control. The prior art does not disclose using antagonists of IL-1R1 in these models, or that they would be efficacious.

Generally, the present antagonists of IL-1R1 will be utilised in purified form together with pharmacologically appropriate carriers. Typically, these carriers include aqueous or alcoholic/aqueous solutions, emulsions or suspensions, any including saline and/or buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride and lactated Ringer's. Suitable physiologically-acceptable adjuvants, if necessary to keep a polypeptide complex in suspension, may be chosen from thickeners such as carboxymethylcellulose, polyvinylpyrrolidone, gelatin and alginates.

Intravenous vehicles include fluid and nutrient replenishers and electrolyte replenishers, such as those based on Ringer's dextrose. Preservatives and other additives, such as antimicrobials, antioxidants, chelating agents and inert gases, may also be present (Mack (1982) *Remington's Pharmaceutical Sciences*, 16th Edition).

A variety of suitable formulations can be used, including extended release formulations.

The antagonists of IL-1R1 may be used as separately administered compositions or in conjunction with other agents. These can include various drugs, such as phosphodiesterase inhibitors (e.g., inhibitors of phosphodiesterase 4), bronchodilators (e.g., beta2-agonists, anticholinergics, theophylline), short-acting beta-agonists (e.g., albuterol, salbutamol, bambuterol, fenoterol, isoetherine, isoproterenol, levalbuterol, metaproterenol, pirbuterol, terbutaline and tornlate), long-acting beta-agonists (e.g., formoterol and salmeterol), short acting anticholinergics (e.g., ipratropium bromide and oxitropium bromide), long-acting anticholinergics (e.g., tiotropium), theophylline (e.g. short acting formulation, long acting formulation), inhaled steroids (e.g., beclomethasone, beclometasone, budesonide, flunisolide, fluticasone propionate and triamcinolone), oral steroids (e.g., methylprednisolone, prednisolone, prednisolon and prednisone), combined short-acting beta-agonists with anticholinergics (e.g., albuterol/salbutamol/ipratropium, and fenoterol/ipratropium), combined long-acting beta-agonists with inhaled steroids (e.g., salmeterol/fluticasone, and formoterol/budesonide) and mucolytic agents (e.g., erdosteine, acetylcysteine, bromheksin, carbocysteine, guaifenesin and iodinated glycerol), cylcosporine, antibiotics, antivirals, methotrexate, adriamycin, cisplatinum, and immunotoxins.

Pharmaceutical compositions can include "cocktails" of various cytotoxic or other agents in conjunction with the antagonist of IL-1R1, or even combinations of antagonists of IL-1R1 having different specificities, such as antagonists of IL-1R1 (e.g., a dAb) selected using different target epitopes, whether or not they are pooled prior to administration.

The antagonists of IL-1R1 can be administered and/or formulated together with one or more additional therapeutic or active agents. When an antagonist of IL-1R1 is administered with an additional therapeutic agent, the antagonist of IL-1R1 can be administered before, simultaneously with or subsequent to administration of the additional agent. Generally, the antagonist of IL-1R1 and additional agent are administered in a manner that provides an overlap of therapeutic effect. In particular

embodiments, the antagonist of IL-1R1 is administered and/or formulated together with an antagonist of TNFR1.

The compositions containing an antagonist of IL-1R1 or a cocktail thereof can be administered for prophylactic and/or therapeutic treatments. In certain
5 therapeutic applications, an amount that is sufficient to accomplish at least partial inhibition, suppression, modulation, killing, or some other measurable parameter, of a population of selected cells is defined as a "therapeutically-effective dose". For example, for treating lung inflammation and/or a respiratory disease, a sputum-inhibiting amount, a bronchial biopsy inflammation-inhibiting amount, a dyspnoea-
10 inhibiting amount, a forced expiratory volume in one second (FEV (1)) increasing amount, an improvement in health status increasing amount, as quantified in a suitable questionnaire such as the St. George's Respiratory Questionnaire (e.g., an improvement score of 4 points).

Amounts needed to achieve these effects will depend upon the severity of the
15 disease and the general state of the patient's own immune system, but generally range from 0.005 to 10.0 mg of antagonist of IL-1R1 *per* kilogram of body weight, with doses of 0.05 to 2.0 mg/kg/dose being more commonly used.

For prophylactic applications, compositions containing the antagonist of IL-1R1 or cocktails thereof may also be administered in similar or slightly lower
20 dosages, to prevent, inhibit or delay onset of disease (e.g., to sustain remission or quiescence, or to prevent acute phase). The skilled clinician will be able to determine the appropriate dosing interval to treat, suppress or prevent disease. When an antagonist of IL-1R1 is administered to treat, suppress or prevent lung inflammation or a respiratory disease, it can be administered up to four times per
25 day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, at a dose off, for example, about 10 µg/kg to about 80 mg/kg, about 100 µg/kg to about 80 mg/kg, about 1 mg/kg to about 80 mg/kg, about 1 mg/kg to about 70 mg/kg, about 1 mg/kg to about 60 mg/kg, about 1 mg/kg to about 50 mg/kg, about 1 mg/kg to about 40 mg/kg, about 1 mg/kg to about 30 mg/kg, about 1 mg/kg
30 to about 20 mg/kg, about 1 mg/kg to about 10 mg/kg, about 10 µg/kg to about 10 mg/kg, about 10 µg/kg to about 5 mg/kg, about 10 µg/kg to about 2.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6

mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg. In particular embodiments, the antagonist of IL-1R1 is administered to treat, suppress or prevent lung inflammation or a respiratory disease each day, every two days, once a week, once every two weeks or once a month at a dose of about 10 µg/kg to about 10 mg/kg (e.g., about 10 µg/kg, about 100 µg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg). The antagonist of IL-1R1 can also be administered to treat, suppress or prevent lung inflammation or a respiratory disease at a daily dose or unit dose of about 10 mg, about 9 mg, about 8 mg, about 7 mg, about 6 mg, about 5 mg, about 4 mg, about 3 mg, about 2 mg or about 1 mg.

Treatment or therapy performed using the antagonist of IL-1R1 described herein is considered "effective" if one or more symptoms are reduced (e.g., by at least 10% or at least one point on a clinical assessment scale), relative to such symptoms present before treatment, or relative to such symptoms in an individual (human or model animal) not treated with such composition or other suitable control. Symptoms will vary depending upon the disease or disorder targeted, but can be measured by an ordinarily skilled clinician or technician. Such symptoms can be measured, for example, by monitoring one or more physical indicators of the disease or disorder (e.g., cellular infiltrate in lung tissue, production of sputum, cellular infiltrate in sputum, dyspnoea, exercise tolerance, spirometry (e.g., forced vital capacity (FVC), force expiratory volume in one second (FEV (1), FEV (1)/FVC), rate or severity of disease exacerbation, or by an accepted clinical assessment scale, for example, the St. George's Respiratory Questionnaire. Suitable clinical assessment scales include, for example, the severity of air flow obstruction according to FEV (1) (*Clinical Guideline 12, Chronic Obstructive Respiratory disease, Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care*, National Institute for Clinical Excellence, London (2004)), Peak Expiratory Flow (PEF) (*British Guideline on the Management of Asthma*, British Thoracic Society, Scottish Intercollegiate Guidelines Network, Revised Edition (2004)), COPD stage according to the American Thoracic Society (ATS) standard (*Am. J. Respir. Crit. Care Med.*, 152:S77-S120 (1995)), asthma impairment class according to the ATS standard (*Am. Rev. Respir. Dis.*, 147:1056-

1061 (1993), or other accepted clinical assessment scale as known in the field. A sustained (e.g., one day or more, preferably longer) reduction in disease or disorder symptoms by at least 10% or by one or more points on a given clinical scale is indicative of "effective" treatment. Similarly, prophylaxis performed using a composition as described herein is "effective" if the onset or severity of one or more symptoms is delayed, reduced or abolished relative to such symptoms in a similar individual (human or animal model) not treated with the composition.

A composition containing an antagonist of IL-1R1 according to the present invention may be utilised in prophylactic and therapeutic settings to aid in the alteration, inactivation, killing or removal of a select target cell population in a mammal. For example, such compositions can be used to reduce levels of inflammatory cells in lung and/or inhibit cell infiltration of the lung.

The antagonists of IL-1R1 can be lyophilised for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and art-known lyophilisation and reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilisation and reconstitution can lead to varying degrees of antibody activity loss (e.g. with conventional immunoglobulins, IgM antibodies tend to have greater activity loss than IgG antibodies) and that use levels may have to be adjusted upward to compensate. The antagonist of IL-1R1 can be lyophilised to form a dry powder for inhalation, and administered in that form.

The route of administration of pharmaceutical compositions according to the invention may be any of those commonly known to those of ordinary skill in the art. The administration can be by any appropriate mode, including parenterally, intravenously, intramuscularly, intraperitoneally, transdermally, *via* the pulmonary route, or by direct infusion with a catheter. The dosage and frequency of administration will depend on the age, sex and condition of the patient, concurrent administration of other drugs, counterindications and other parameters to be taken into account by the clinician. Administration can be local (e.g., local delivery to the lung by pulmonary administration, e.g., intranasal administration) or systemic as indicated.

In particular embodiments, an antagonist of IL-1R1 is administered via pulmonary delivery, such as by inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops) or by systemic delivery (e.g., parenteral, intravenous, intramuscular, intraperitoneal, subcutaneous). In preferred embodiments, the
5 antagonist of IL-1R1 is administered to a subject via pulmonary administration, such as inhalation or intranasal administration (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops). For inhalation, the antagonist of IL-1R1 can be administered with the use of a nebulizer, inhaler, atomizer, aerosolizer, mister, dry powder inhaler, metered dose inhaler, metered dose sprayer, metered dose mister,
10 metered dose atomizer, or other suitable delivery device.

The invention relates to a method for treating, suppressing or preventing lung inflammation or a respiratory disease, comprising administering to a subject in need thereof an effective amount of an antagonist of IL-1R1. In some embodiments, the effective amount administered does not exceed about 10 mg/kg/day, and preferably
15 the level of inflammatory cells in the lung is reduced relative to pretreatment levels, or recruitment of inflammatory cells into the lung is inhibited relative to pretreatment levels. The level of inflammatory cells in the lung or recruitment of inflammatory cells into the lung can be reduced or inhibited relative to pretreatment levels by at least about 30%, at least about 40%, at least about 50%, at least about
20 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%.

The level of inflammatory cells in the lung or recruitment of inflammatory cells into the lung can be reduced or inhibited relative to pretreatment levels with $p < 0.05$ or $p < 0.001$, in some embodiments. Preferably, statistical analysis and
25 significance is determined using the methods described herein.

Levels of cells (e.g., inflammatory cells) in the lung can be assessed using any suitable method, such as total or differential cell counts (e.g., macrophage cell count, neutrophil cell count, eosinophil cell count, lymphocyte cell count, epithelial cell count) in BAL, sputum or biopsy (e.g., bronchial biopsy, lung biopsy).
30

In some embodiments, the methods described herein are employed for treating, suppressing or preventing chronic obstructive respiratory disease (e.g., chronic bronchitis, chronic obstructive bronchitis, emphysema), asthma (e.g., steroid

resistant asthma), pneumonia (e.g., bacterial pneumonia, such as Staphylococcal pneumonia), or lung inflammation.

The invention also relates to the use of an antagonist of IL-1R1, as described herein, for the manufacture of a medicament or formulation for treating lung
5 inflammation or a respiratory disease described herein. The medicament can be for systemic administration and/or local administration to pulmonary tissue.

The invention provides methods of treating a respiratory disease in which a therapeutically effective amount of an antagonist of IL-1R1 (e.g., IL-1ra, dAb, ligand) is administered systemically to a subject in need. In some embodiments, the
10 method further comprises administering a therapeutically effective amount of an antagonist of TNFR1 to the subject. The antagonist of TNFR1 can be administered by any suitable method, such as by pulmonary administration or systemic administration.

15 Antagonists of IL-1R1

Antagonists of IL-1R1 suitable for use in the invention include, for example, small molecules, proteins, polypeptides (e.g., fusion proteins), peptides and conjugates that bind IL-1R1 and inhibit a function of IL-1R1 (e.g., binding of IL-1 α and/or IL-1 β ; inhibit signaling upon binding of IL-1 α and/or IL-1 β). As described
20 herein, an antagonist of IL-1R1 suitable for use in the invention comprise an antagonist of IL-1R1 moiety, that can be formatted into a variety of suitable structures. For example, antagonists of IL-1R1 include proteins or polypeptides that comprise IL-1ra or functional variants of IL-1ra, and proteins, polypeptides and peptides that comprise a binding domain that has a binding site with binding
25 specificity for IL-1R1 and inhibits a function of IL-1R1. Preferably, the binding domain that has a binding site with binding specificity for IL1-R1 and inhibits a function of IL-1R1 is an antibody that bind IL-1R1 or an antigen-binding fragment thereof, such as, Fab fragment, Fab' fragment, F(ab')₂ fragment, Fv fragment (e.g., single chain Fv (scFv), disulfide bonded Fv fragment), domain antibody (dAbs;
30 single V_H, single V_K, single V_L), *Camelid* V_{HH} and the like. The binding domain can comprises one or more complementarity determining regions (CDRs) of an immunoglobulin single variable domain that has binding specificity for IL-1R1 in a

suitable format, such that the binding domain has binding specificity for IL-1R1. For example, the CDRs can be grafted onto a suitable protein scaffold or skeleton, such as an affibody, an SpA scaffold, an LDL receptor class A domain, or an EGF domain. The binding domain can also be a protein domain comprising a binding site
5 for IL-1R1, *e.g.*, a protein domain is selected from an affibody, an SpA domain, an LDL receptor class A domain an EGF domain, an avimer (see, *e.g.*, U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301).

In some embodiments, the antagonist of IL-1R1 comprises a non-immunoglobulin binding moiety that has binding specificity for IL-1R1 and inhibits
10 a function of IL-1R1, wherein the non-immunoglobulin binding moiety comprises one, two or three of the CDRs of a V_H , V_L or V_{HH} that binds IL-1R1 and a suitable scaffold. In certain embodiments, the non-immunoglobulin binding moiety comprises CDR3 but not CDR1 or CDR2 of a V_H , V_L or V_{HH} that binds IL-1R1 and a suitable scaffold. In other embodiments, the non-immunoglobulin binding moiety
15 comprises CDR1 and CDR2, but not CDR3 of a V_H , V_L or V_{HH} that binds IL-1R1 and a suitable scaffold. In other embodiments, the non-immunoglobulin binding moiety comprises CDR1, CDR2 and CDR3 of a V_H , V_L or V_{HH} that binds IL-1R1 and a suitable scaffold. In other embodiments, the antagonist of IL-1R1 comprises only CDR3 of a V_H , V_L or V_{HH} that binds IL-1R1. Preferably, the CDR or CDRs of
20 the antagonist of IL-1R1 of these embodiments is a CDR or CDRs of a V_H , or V_L that binds IL-1R1 described herein.

Suitable antagonists of IL-1R1 for use in the invention also include conjugates, such as a covalent antagonist of IL-1R1 conjugates, and a noncovalent antagonists of IL-1R1 conjugates, and fusion proteins, such as, an antagonist of IL-
25 1R1 fusion, as defined herein. For example, the antagonist of IL-1R1 can be a fusion protein that that comprise IL-1ra, a functional variant of IL-1ra, an antibody that bind IL-1R1, an antigen-binding fragment of an antibody that binds IL-1R1 (*e.g.*, a dAb), and/or a non-immunoglobulin binding moiety that has binding specificity for IL-1R1.

30 Preferred antagonists of IL-1R1 are polypeptides that comprise IL-1ra or functional variants of IL-1ra, and polypeptides that comprise a dAb that binds IL-1R1 and inhibits a function of IL-1R1.

Antibodies and Antibody Portions that bind IL-1R1

The antagonist of IL-1R1 can comprise an (*i.e.*, one or more) antibody or antigen-binding fragment of an antibody that binds IL-1R1 and inhibits function of IL-1R1. For example, the antibody or antigen-binding fragment thereof can bind IL-1R1 and inhibiting binding of a ligand (*e.g.*, IL-1 α , IL-1 β , IL-1ra, or any combination of the foregoing) to the receptor, or inhibit IL-1R1 mediated signaling upon binding of a ligand (*e.g.*, IL-1 α , IL-1 β). The antibody or antigen-binding fragment can have binding specificity for IL-1R1 of an animal to which the antagonist of IL-1R1 will be administered. Preferably, the antibody or antigen-binding fragment has binding specificity for human IL-1R1. However, veterinary applications are contemplated and the antibody or antigen-binding fragment can have binding specificity for IL-1R1 from a desired animal, for example IL-1R1 from dog, cat, horse, cow, chicken, sheep, pig, goat, deer, mink, and the like. In some embodiments, the antibody or antigen-binding fragment has binding specificity for IL-1R1 from more than one species. Such antibodies or antigen-binding fragment provide the advantage of allowing preclinical and clinical studies to be designed and executed using the same antagonist of IL-1R1, and obviate the need to conduct preclinical studies with a suitable surrogate antagonist of IL-1R1.

Antibodies and antigen-binding fragments thereof which bind a desired IL-1R1 (*e.g.*, human IL-1R1) can be selected from a suitable collection of natural or artificial antibodies or raised against an appropriate immunogen in a suitable host. For example, antibodies can be raised by immunizing a suitable host (*e.g.*, mouse, human antibody-transgenic mouse, rat, rabbit, chicken, goat, non-human primate (*e.g.*, monkey)) with IL-1R1 (*e.g.*, isolated or purified human IL-1R1) or a peptide of IL-1R1 (*e.g.*, a peptide comprising at least about 8, 9, 10, 11, 12, 15, 20, 25, 30, 33, 35, 37, or 40 amino acid residues). Antibodies and antigen-binding fragments that bind IL-1R1 can also be selected from a library of recombinant antibodies or antigen-binding fragments, such as a phage display library. Such libraries can contain antibodies or antigen-binding fragments of antibodies that contain natural or artificial amino acid sequences. For example, the library can contain Fab fragments which contain artificial CDRs (*e.g.*, random amino acid sequences) and human

framework regions. (See, for example, U.S. Patent No. 6,300,064 (Knappik, *et al.*).) In other examples, the library contains scFv fragments or dAbs (single V_H, single V_κ or single V_λ) with sequence diversity in one or more CDRs. (See, *e.g.*, WO 99/20749 (Tomlinson and Winter), WO 03/002609 A2 (Winter *et al.*), WO 5 2004/003019A2 (Winter *et al.*).)

Antigen-binding fragments of antibodies that are suitable for use in the invention include, for example, Fab fragments, Fab' fragments, F(ab')₂ fragments, Fv fragments (including single chain Fv (scFv) and disulfide bonded Fv), a single variable domain (V_H, V_L, V_{HH}). Such antigen-binding fragments can be produced 10 using any suitable method, such as by proteolysis of an antibody using pepsin, papain or other protease having the requisite cleavage specificity, or using recombinant techniques. For example, Fv fragments can be prepared by digesting an antibody with a suitable protease or using recombinant DNA technology. For example, a nucleic acid can be prepared that encodes a light chain variable region 15 and heavy chain variable region that are connected by a suitable peptide linker, such as a chain of two to about twenty Glycyl residues or (Gly₄Ser)_n, where n = from 1 to 8, *e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8. The nucleic acid can be introduced into a suitable host (*e.g.*, *E. coli*) using any suitable technique (*e.g.*, transfection, transformation, infection), and the host can be maintained under conditions suitable for expression 20 of a single chain Fv fragment. A variety of antigen-binding fragments of antibodies can be prepared using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, an expression construct encoding a F(ab')₂ portion of an immunoglobulin heavy chain can be designed by introducing a translation stop codon at the 3' end of the sequence encoding the hinge 25 region of the heavy chain. The antagonist of IL-1R1 can comprise the individual heavy and light chains of antibodies that bind IL-1R1 or portions of the individual chains that bind IL-1R1 (*e.g.*, a single V_H, V_κ or V_λ).

Suitable antibodies and antigen-binding fragments thereof that bind IL-1R1 include, for example, human antibodies and antigen-binding fragments thereof, 30 humanized antibodies and antigen-binding fragments thereof, chimeric antibodies and antigen-binding fragments thereof, rodent (*e.g.*, mouse, rat) antibodies and antigen-binding fragments thereof, and *Camelid* antibodies and antigen-binding

fragments thereof. In certain embodiments, the antagonist of IL-1R1 comprises a *Camelid* V_{HH} that binds IL-1R1. *Camelid* V_{HHS} are immunoglobulin single variable domain polypeptides which are derived from heavy chain antibodies that are naturally devoid of light chains. Such antibodies occur in *Camelid* species including
5 camel, llama, alpaca, dromedary, and guanaco. V_{HH} molecules are about ten times smaller than IgG molecules, and as single polypeptides, are very stable and resistant to extreme pH and temperature conditions.

If antibodies are prepared by immunization, preparation of the immunizing antigen, and polyclonal and monoclonal antibody production can be performed using
10 any suitable technique. A variety of methods have been described. (See, *e.g.*, Kohler *et al.*, *Nature*, 256: 495-497 (1975) and *Eur. J. Immunol.* 6: 511-519 (1976); Milstein *et al.*, *Nature* 266: 550-552 (1977); Koprowski *et al.*, U.S. Patent No. 4,172,124; Harlow, E. and D. Lane, 1988, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory: Cold Spring Harbor, NY); *Current Protocols In*
15 *Molecular Biology*, Vol. 2 (Supplement 27, Summer '94), Ausubel, F.M. *et al.*, Eds., (John Wiley & Sons: New York, NY), Chapter 11, (1991).) When a monoclonal antibody is desired, a hybridoma can be produced by fusing suitable cells from an immortal cell line (*e.g.*, a myeloma cell line such as SP2/0, P3X63Ag8.653 or a heteromyeloma) with antibody-producing cells. Antibody-producing cells can be
20 obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans, human-antibody transgenic animals or other suitable animals immunized with the antigen of interest. Cells that produce antibodies of human origin (*e.g.*, a human antibody) can be produced using suitable methods, for example, fusion of a human antibody-producing cell and a heteromyeloma or trioma, or immortalization
25 of an activated human B cell via infection with Epstein Barr virus. (See, *e.g.*, U.S. Patent No. 6,197,582 (Trakht); Niedbala *et al.*, *Hybridoma*, 17:299-304 (1998); Zanella *et al.*, *J Immunol Methods*, 156:205-215 (1992); Gustafsson *et al.*, *Hum Antibodies Hybridomas*, 2:26-32 (1991).) The fused or immortalized antibody-producing cells (hybridomas) can be isolated using selective culture conditions, and
30 cloned by limiting dilution. Cells which produce antibodies with the desired specificity can be identified using a suitable assay (*e.g.*, ELISA).

Antibodies also can be prepared directly (*e.g.*, synthesized or cloned) from an isolated antigen-specific antibody producing cell (*e.g.*, a cell from the peripheral blood or, preferably the spleen or lymph nodes determined to produce an antibody with desired specificity), of humans, human-antibody transgenic animals or other
5 suitable animals immunized with the antigen of interest (see, *e.g.*, U.S. Patent No. 5,627,052 (Schrader)).

When the antagonist of IL-1R1 is for administration to a human, any antibody or antigen-binding fragment of an antibody that is part of the antagonists of IL-1R1 (*e.g.*, an antibody or antigen-binding fragment thereof that binds IL-1R1
10 (*e.g.*, human IL-1R1) or serum albumin (*e.g.*, human serum albumin)) can be a human, humanized or chimeric antibody or an antigen-binding fragment of such an antibody. These types of antibodies and antigen-binding fragments are less immunogenic or non-immunogenic in humans and provide well-known advantages. For example, antagonists of IL-1R1 that comprise an antigen-binding fragment of a
15 human, humanized or chimeric antibody can be administered repeatedly to a human with less or no loss of efficacy (compared with other fully immunogenic antibodies) due to the elaboration of human antibodies that bind to the antagonist of IL-1R1. When the antagonist of IL-1R1 is intended for veterinary administration, analogous antibodies or antigen-binding fragments can be used. For example, CDRs from a
20 murine or human antibody can be grafted onto framework regions from a desired animal, such as a horse or cow.

Human antibodies and nucleic acids encoding same can be obtained, for example, from a human or from human-antibody transgenic animals. Human-antibody transgenic animals (*e.g.*, mice) are animals that are capable of producing a
25 repertoire of human antibodies, such as XENOMOUSE (Abgenix, Fremont, CA), HUMAB-MOUSE, KIRIN TC MOUSE or KM-MOUSE (MEDAREX, Princeton, NJ). Generally, the genome of human-antibody transgenic animals has been altered to include a transgene comprising DNA from a human immunoglobulin locus that can undergo functional rearrangement. An endogenous immunoglobulin locus in a
30 human-antibody transgenic animal can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by an endogenous gene. Suitable methods for producing human-antibody transgenic animals are well known

in the art. (See, for example, U.S. Pat. Nos. 5,939,598 and 6,075,181 (Kucherlapati *et al.*), U.S. Pat. Nos. 5,569,825, 5,545,806, 5,625,126, 5,633,425, 5,661,016, and 5,789,650 (Lonberg *et al.*), Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA*, 90: 2551-2555 (1993), Jakobovits *et al.*, *Nature*, 362: 255-258 (1993), Jakobovits *et al.* WO 98/50433, Jakobovits *et al.* WO 98/24893, Lonberg *et al.* WO 98/24884, Lonberg *et al.* WO 97/13852, Lonberg *et al.* WO 94/25585, Lonberg *et al.* EP 0 814 259 A2, Lonberg *et al.* GB 2 272 440 A, Lonberg *et al.*, *Nature* 368:856-859 (1994), Lonberg *et al.*, *Int Rev Immunol* 13(1):65-93 (1995), Kucherlapati *et al.* WO 96/34096, Kucherlapati *et al.* EP 0 463 151 B1, Kucherlapati *et al.* EP 0 710 719 A1, Surani *et al.* US. Pat. No. 5,545,807, Bruggemann *et al.* WO 90/04036, Bruggemann *et al.* EP 0 438 474 B1, Taylor *et al.*, *Int. Immunol.* 6(4):579-591 (1994), Taylor *et al.*, *Nucleic Acids Research* 20(23):6287-6295 (1992), Green *et al.*, *Nature Genetics* 7:13-21 (1994), Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Tuaillon *et al.*, *Proc Natl Acad Sci USA* 90(8):3720-3724 (1993) and Fishwild *et al.*, *Nat Biotechnol* 14(7):845-851 (1996), the teachings of each of the foregoing are incorporated herein by reference in their entirety.)

Human-antibody transgenic animals can be immunized with a suitable antigen (*e.g.*, human IL-1R1), and antibody producing cells can be isolated and fused to form hybridomas using conventional methods. Hybridomas that produce human antibodies having the desired characteristics (*e.g.*, specificity, affinity) can be identified using any suitable assay (*e.g.*, ELISA) and, if desired, selected and subcloned using suitable culture techniques.

Humanized antibodies and other CDR-grafted antibodies can be prepared using any suitable method. The CDRs of a CDR-grafted antibody can be derived from a suitable antibody which binds a serum albumin (referred to as a donor antibody). Other sources of suitable CDRs include natural and artificial serum albumin-specific antibodies obtained from human or nonhuman sources, such as rodent (*e.g.*, mouse, rat, rabbit), chicken, pig, goat, non-human primate (*e.g.*, monkey) or a library.

The framework regions of a humanized antibody are preferably of human origin, and can be derived from any human antibody variable region having sequence similarity to the analogous or equivalent region (*e.g.*, heavy chain variable

region or light chain variable region) of the antigen-binding region of the donor antibody. Other sources of framework regions of human origin include human variable region consensus sequences. (See, *e.g.*, Kettleborough, C.A. *et al.*, *Protein Engineering* 4:773-783 (1991); Carter *et al.*, WO 94/04679; Kabat, E.A., *et al.*,
5 *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, U.S. Government Printing Office (1991)). Other types of CDR grafted antibodies can contain framework regions of suitable origin, such as framework regions encoded by germline antibody gene segments from horse, cow, dog, cat and the like.

10 Framework regions of human origin can include amino acid substitutions or replacements, such as "back mutations" which replace an amino acid residue in the framework region of human or animal origin with a residue from the corresponding position of the donor antibody. One or more mutations in the framework region can be made, including deletions, insertions and substitutions of one or more amino
15 acids. Variants can be produced by a variety of suitable methods, including mutagenesis of nonhuman donor or acceptor human chains. (See, *e.g.*, U.S. Patent Nos. 5,693,762 (Queen *et al.*) and 5,859,205 (Adair *et al.*), the entire teachings of which are incorporated herein by reference.)

Constant regions of antibodies, antibody chains (*e.g.*, heavy chain, light
20 chain) or fragments or portions thereof, if present, can be derived from any suitable source. For example, constant regions of human, humanized and certain chimeric antibodies, antibody chains (*e.g.*, heavy chain, light chain) or fragments or portions thereof, if present can be of human origin and can be derived from any suitable human antibody or antibody chain. For example, a constant region of human origin
25 or portion thereof can be derived from a human κ or λ light chain, and/or a human γ (*e.g.*, $\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$), μ , α (*e.g.*, $\alpha 1$, $\alpha 2$), δ or ϵ heavy chain, including allelic variants. In certain embodiments, the antibody or antigen-binding fragment (*e.g.*, antibody of human origin, human antibody) can include amino acid substitutions or replacements that alter or tailor function (*e.g.*, effector function). For example, a
30 constant region of human origin (*e.g.*, $\gamma 1$ constant region, $\gamma 2$ constant region) can be designed to reduce complement activation and/or Fc receptor binding. (See, for example, U.S. Patent Nos. 5,648,260 (Winter *et al.*), 5,624,821 (Winter *et al.*) and

5,834,597 (Tso *et al.*), the entire teachings of which are incorporated herein by reference.) Preferably, the amino acid sequence of a constant region of human origin that contains such amino acid substitutions or replacements is at least about 95% identical over the full length to the amino acid sequence of the unaltered
5 constant region of human origin, more preferably at least about 99% identical over the full length to the amino acid sequence of the unaltered constant region of human origin.

Humanized antibodies, CDR grafted antibodies or antigen-binding fragments of a humanized or CDR grafted antibody can be prepared using any suitable method.
10 Several such methods are well-known in the art. (See, *e.g.*, U.S. Patent No. 5,225,539 (Winter), U.S. Patent No. 5,530,101 (Queen *et al.*).) The portions of a humanized or CDR grafted antibody (*e.g.*, CDRs, framework, constant region) can be obtained or derived directly from suitable antibodies (*e.g.*, by *de novo* synthesis of a portion), or nucleic acids encoding an antibody or chain thereof having the
15 desired property (*e.g.*, binds serum albumin) can be produced and expressed. To prepare a portion of a chain, one or more stop codons can be introduced at the desired position. For example, nucleic acid (*e.g.*, DNA) sequences coding for humanized or CDR grafted variable regions can be constructed using PCR mutagenesis methods to alter existing DNA sequences. (See, *e.g.*, Kamman, M., *et al.*, *Nucl. Acids Res.* 17:5404 (1989).) PCR primers coding for the new CDRs can be hybridized to a DNA template of a previously humanized variable region which is based on the same, or a very similar, human variable region (Sato, K., *et al.*, *Cancer Research* 53:851-856 (1993)). If a similar DNA sequence is not available for use as a template, a nucleic acid comprising a sequence encoding a variable
25 region sequence can be constructed from synthetic oligonucleotides (see *e.g.*, Kolbinger, F., *Protein Engineering* 8:971-980 (1993)). A sequence encoding a signal peptide can also be incorporated into the nucleic acid (*e.g.*, on synthesis, upon insertion into a vector). The natural signal peptide sequence from the acceptor antibody, a signal peptide sequence from another antibody or other suitable
30 sequence can be used (see, *e.g.*, Kettleborough, C.A., *Protein Engineering* 4:773-783 (1991)). Using these methods or other suitable methods, variants can be readily produced. In one embodiment, cloned variable regions can be mutated, and

sequences encoding variants with the desired specificity can be selected (*e.g.*, from a phage library; see, *e.g.*, U.S. Patent No. 5,514,548 (Krebber *et al.*) and WO 93/06213 (Hoogenboom *et al.*)).

5 The antibody or antigen-binding fragment that binds IL-1R1 can be a chimeric antibody or an antigen-binding fragment of a chimeric antibody. The chimeric antibody or antigen-binding fragment thereof comprises a variable region from one species (*e.g.*, mouse) and at least a portion of a constant region from another species (*e.g.*, human). Chimeric antibodies and antigen-binding fragments of chimeric antibodies can be prepared using any suitable method. Several suitable
10 methods are well-known in the art. (See, *e.g.*, U.S. Patent No. 4,816,567 (Cabilly *et al.*), U.S. Patent No. 5,116,946 (Capon *et al.*).)

A preferred method for obtaining antigen-binding fragments of antibodies that bind IL-1R1 comprises selecting an antigen-binding fragment (*e.g.*, scFvs, dAbs) that has binding specificity for a desired IL-1R1 from a repertoire of antigen-
15 binding fragments. For example, dAbs that bind IL-1R1 can be selected from a suitable phage display library. A number of suitable bacteriophage display libraries and selection methods (*e.g.*, monovalent display and multivalent display systems) have been described. (See, *e.g.*, Griffiths *et al.*, U.S. Patent No. 6,555,313 B1 (incorporated herein by reference); Johnson *et al.*, U.S. Patent No. 5,733,743
20 (incorporated herein by reference); McCafferty *et al.*, U.S. Patent No. 5,969,108 (incorporated herein by reference); Mulligan-Kehoe, U.S. Patent No. 5,702,892 (incorporated herein by reference); Winter, G. *et al.*, *Annu. Rev. Immunol.* 12:433-455 (1994); Soumillion, P. *et al.*, *Appl. Biochem. Biotechnol.* 47(2-3):175-189 (1994); Castagnoli, L. *et al.*, *Comb. Chem. High Throughput Screen*, 4(2):121-133
25 (2001); WO 99/20749 (Tomlinson and Winter); WO 03/002609 A2 (Winter *et al.*); WO 2004/003019A2 (Winter *et al.*).) The polypeptides displayed in a bacteriophage library can be displayed on any suitable bacteriophage, such as a filamentous phage (*e.g.*, fd, M13, F1), a lytic phage (*e.g.*, T4, T7, lambda), or an RNA phage (*e.g.*, MS2), for example, and selected for binding to IL-1R1 (*e.g.*, human IL-1R1).

30 Generally, a library of phage that displays a repertoire of polypeptides as fusion proteins with a suitable phage coat protein is used. Such a library can be produced using any suitable methods, such as introducing a library of phage vectors

or phagemid vectors encoding the displayed antibodies or antigen-binding fragments thereof into suitable host bacteria, and culturing the resulting bacteria to produce phage (*e.g.*, using a suitable helper phage or complementing plasmid if desired). The library of phage can be recovered from such a culture using any suitable
5 method, such as precipitation and centrifugation.

The library can comprise a repertoire of antibodies or antigen-binding fragments thereof that contains any desired amount of amino acid sequence diversity. For example, the repertoire can contain antibodies or antigen-binding fragments thereof that have amino acid sequences that correspond to naturally
10 occurring antibodies from a desired organism, and/or can contain one or more regions of random or randomized amino acid sequences (*e.g.*, CDR sequences). The antibodies or antigen-binding fragments thereof in such a repertoire or library can comprise defined regions of random or randomized amino acid sequence and regions of common amino acid sequence. In certain embodiments, all or substantially all
15 polypeptides in a repertoire are a desired type of antigen-binding fragment of an antibody (*e.g.*, human V_H or human V_L). For example, each polypeptide in the repertoire can contain a V_H, a V_L or an Fv (*e.g.*, a single chain Fv).

Amino acid sequence diversity can be introduced into any desired region of antibodies or antigen-binding fragments thereof using any suitable method. For
20 example, amino acid sequence diversity can be introduced into a target region, such as a complementarity determining region of an antibody variable domain, by preparing a library of nucleic acids that encode the diversified antibodies or antigen-binding fragments thereof using any suitable mutagenesis methods (*e.g.*, low fidelity PCR, oligonucleotide-mediated or site directed mutagenesis, diversification using
25 NNK codons) or any other suitable method. If desired, a region of the antibodies or antigen-binding fragments thereof to be diversified can be randomized.

A suitable phage display library can be used to select antibodies or antigen-binding fragments of antibodies that bind IL-1R1, inhibit IL-1R1 function and have other beneficial properties. For example, antibodies or antigen-binding fragments
30 that resist aggregation when unfolded can be selected. Aggregation is influenced by polypeptide concentration and is thought to arise in many cases from partially folded or unfolded intermediates. Factors and conditions that favor partially folded

intermediates, such as elevated temperature and high polypeptide concentration, promote irreversible aggregation. (Fink, A.L., *Folding & Design* 3:R1-R23 (1998).) For example, storing purified polypeptides in concentrated form, such as a lyophilized preparation, frequently results in irreversible aggregation of at least a portion of the polypeptides. Also, production of a polypeptide by expression in biological systems, such as *E. coli*, often results in the formation of inclusion bodies which contain aggregated polypeptides. Recovering active polypeptides from inclusion bodies can be very difficult and require adding additional steps, such as a refolding step, to a biological production system.

Antibodies and antigen-binding fragments that resist aggregation and unfold reversibly when heated can be selected from a suitable phage display library. Generally, a phage display library comprising a repertoire of displayed antibodies or antigen-binding fragments thereof is heated to a temperature (T_s) at which at least a portion of the displayed antibodies or antigen-binding fragments thereof are unfolded, then cooled to a temperature (T_c) wherein $T_s > T_c$, whereby at least a portion of the antibodies or antigen-binding fragments thereof have refolded and a portion of the polypeptides have aggregated. Then, antibodies or antigen-binding fragments thereof that unfold reversibly and bind serum albumin are recovered at a temperature (T_r). The recovered antibody or antigen-binding fragment thereof that unfolds reversibly has a melting temperature (T_m), and preferably, the repertoire was heated to T_s , cooled to T_c and the antibody or antigen-binding fragment thereof that unfolds reversibly was isolated at T_r , such that $T_s > T_m > T_c$, and $T_s > T_m > T_r$. Generally, the phage display library is heated to about 80°C and cooled to about room temperature or about 4°C before selection. Antibodies or antigen-binding fragment thereof that unfold reversibly and resist aggregation can also be designed or engineered by replacing certain amino acid residue with residues that confer the ability to unfold reversibly. (See, WO 2004/101790 (Jespers *et al.*), and U.S. Provisional Patent Application Nos: 60/470,340 (filed on May 14, 2003) and 60/554,021 (filed on March 17, 2004) for detailed discussion of methods for selecting and for designing or engineering antibodies or antigen-binding fragments thereof that unfold reversibly. The teachings of WO 2004/101790 and both of the

foregoing U.S. Provisional Patent Applications are incorporated herein by reference.)

Antibodies or antigen-binding fragments thereof that unfold reversibly and resist aggregation provide several advantages. For example, due to their resistance to aggregation, antibodies or antigen-binding fragments thereof that unfold reversibly can readily be produced in high yield as soluble proteins by expression using a suitable biological production system, such as *E. coli*. In addition, antibodies or antigen-binding fragments thereof that unfold reversibly can be formulated and/or stored at higher concentrations than conventional polypeptides, and with less aggregation and loss of activity. For example, dAb HEL4 is a human V_H that binds hen egg lysozyme and unfolds reversibly, and DOM7h-26 (SEQ ID NO: 743) is a human V_H that binds serum albumin and unfolds reversibly.

Preferably, the antibody or antigen-binding fragment thereof that binds IL-1R1 comprises a variable domain (V_H, V_K, V_L) in which one or more of the framework regions (FR) comprise (a) the amino acid sequence of a human framework region, (b) at least 8 contiguous amino acids of the amino acid sequence of a human framework region, or (c) an amino acid sequence encoded by a human germline antibody gene segment, wherein said framework regions are as defined by Kabat. In certain embodiments, the amino acid sequence of one or more of the framework regions is the same as the amino acid sequence of a corresponding framework region encoded by a human germline antibody gene segment, or the amino acid sequences of one or more of said framework regions collectively comprise up to 5 amino acid differences relative to the amino acid sequence of said corresponding framework region encoded by a human germline antibody gene segment.

In other embodiments, the amino acid sequences of FR1, FR2, FR3 and FR4 are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment, or the amino acid sequences of FR1, FR2, FR3 and FR4 collectively contain up to 10 amino acid differences relative to the amino acid sequences of corresponding framework regions encoded by said human germline antibody gene segments. In other embodiments, the amino acid sequence of said FR1, FR2 and FR3 are the same as the amino acid sequences

of corresponding framework regions encoded by said human germline antibody gene segment.

In particular embodiments, the antibody or antigen binding fragment that binds IL-1R1 comprises an immunoglobulin variable domain (*e.g.*, V_H , V_L) based on a human germline sequence, and if desired can have one or more diversified regions, such as the complementarity determining regions. Suitable human germline sequence for V_H include, for example, sequences encoded by the V_H gene segments DP4, DP7, DP8, DP9, DP10, DP31, DP33, DP45, DP46, DP47, DP49, DP50, DP51, DP53, DP54, DP65, DP66, DP67, DP68 and DP69, and the J_H segments JH1, JH2, JH3, JH4, JH4b, JH5 and JH6. Any of the foregoing V_H gene segments can be paired with any of the foregoing J_H segments. Suitable human germline sequence for V_L include, for example, sequences encoded by the V_K gene segments DPK1, DPK2, DPK3, DPK4, DPK5, DPK6, DPK7, DPK8, DPK9, DPK10, DPK12, DPK13, DPK15, DPK16, DPK18, DPK19, DPK20, DPK21, DPK22, DPK23, DPK24, DPK25, DPK26 and DPK 28, and the J_K segments J_K 1, J_K 2, J_K 3, J_K 4 and J_K 5. Any of the foregoing V_L gene segments can be paired with any of the foregoing J_K segments.

The antibody or antigen-binding fragment that bind IL-1R1 can bind IL-1R1 with any desired affinity, and antibodies and antigen-binding fragments with a desired affinity can be readily identified using any suitable screening method. The antibody or antigen-binding fragment that binds IL-1R1 (*e.g.*, dAb) generally binds with a K_D ($K_D = K_{off}(k_d)/K_{on}(k_a)$) of about K_D of 300 nM to 5 pM (ie, 3×10^{-7} to 5×10^{-12} M), preferably 50 nM to 20 pM, more preferably 5 nM to 200 pM and most preferably 1 nM to 100 pM, for example 1×10^{-7} M or less, preferably 1×10^{-8} M or less, more preferably 1×10^{-9} M or less, advantageously 1×10^{-10} M or less and most preferably 1×10^{-11} M or less; and/or a K_{off} rate constant of $5 \times 10^{-1} \text{ s}^{-1}$ to $1 \times 10^{-7} \text{ s}^{-1}$, preferably $1 \times 10^{-2} \text{ s}^{-1}$ to $1 \times 10^{-6} \text{ s}^{-1}$, more preferably $5 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, for example $5 \times 10^{-1} \text{ s}^{-1}$ or less, preferably $1 \times 10^{-2} \text{ s}^{-1}$ or less, advantageously $1 \times 10^{-3} \text{ s}^{-1}$ or less, more preferably $1 \times 10^{-4} \text{ s}^{-1}$ or less, still more preferably $1 \times 10^{-5} \text{ s}^{-1}$ or less, and most preferably $1 \times 10^{-6} \text{ s}^{-1}$ or less as determined by surface plasmon resonance. Certain antibody or antigen-binding fragment that bind IL-1R1, specifically bind

human IL-1R1 with a K_D of 50 nM to 20 pM, and a K_{off} rate constant of $5 \times 10^{-1} \text{ s}^{-1}$ to $1 \times 10^{-7} \text{ s}^{-1}$, as determined by surface plasmon resonance.

Preferably, the antibody or antigen-binding fragment that bind IL-1R1 inhibits binding of IL-1 α and/or IL-1 β to IL-1R1 with an inhibitory concentration 50 (IC₅₀) that is $\leq 10 \text{ }\mu\text{M}$, $\leq 1 \text{ }\mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 500 \text{ pM}$, $\leq 300 \text{ pM}$, $\leq 100 \text{ pM}$, or $\leq 10 \text{ pM}$. The IC₅₀ is preferably determined using an *in vitro* receptor binding assay, such as the assay described herein.

It is also preferred that the antibody or antigen-binding fragment that bind IL-1R1 inhibits IL-1 α and/or IL-1 β -induced functions in a suitable *in vitro* assay with a neutralizing dose 50 (ND₅₀) that is $\leq 10 \text{ }\mu\text{M}$, $\leq 1 \text{ }\mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 500 \text{ pM}$, $\leq 300 \text{ pM}$, $\leq 100 \text{ pM}$, or $\leq 10 \text{ pM}$. For example, the antibody or antigen-binding fragment that bind IL-1R1 can inhibit IL-1 α - or IL-1 β -induced release of Interleukin-8 by MRC-5 cells (ATCC Accession No. CCL-171) in an *in vitro* assay, such as the assay described herein. In another example, the antibody or antigen-binding fragment that bind IL-1R1 can inhibit IL-1 α - or IL-1 β -induced release of Interleukin-6 in a whole blood assay, such as the assay described herein.

In particular embodiments, the antagonist of IL-1R1 comprises an antagonist of IL-1R1 moiety that is a dAb. For example, the antagonist of IL-1R1 comprises a dAb that competes with a dAb for binding to IL-1R1, wherein the dAb is selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36

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DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

In other embodiments, the antagonists of IL-1R1 comprises a dAb having an amino acid sequence that has at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70),

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Amino acid sequence identity is preferably determined using a suitable sequence alignment algorithm and default parameters, such as BLAST P (Karlin and Altschul, *Proc. Natl. Acad. Sci. USA* 87(6):2264-2268 (1990)).

In other embodiments, the antagonists of IL-1R1 comprises a e that has an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ

ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23),

5 DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37),

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NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102),
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10 DOM4-129-25 (SEQ ID NO:197), DOM4-129-26 (SEQ ID NO:198), DOM4-129-
27 (SEQ ID NO:199), DOM4-129-28 (SEQ ID NO:200), DOM4-129-29 (SEQ ID
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DOM4-129-33 (SEQ ID NO:204), DOM4-129-34 (SEQ ID NO:205), DOM4-129-
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DOM4-129-41 (SEQ ID NO:211), DOM4-129-42 (SEQ ID NO:212), DOM4-129-
43 (SEQ ID NO:213), DOM4-129-44 (SEQ ID NO:214), DOM4-130 (SEQ ID
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DOM4-130-3 (SEQ ID NO:218), DOM4-130-4 (SEQ ID NO:219), DOM4-130-5
20 (SEQ ID NO:220), DOM4-130-6 (SEQ ID NO:221), DOM4-130-7 (SEQ ID
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DOM4-130-10 (SEQ ID NO:225), DOM4-130-11 (SEQ ID NO:226), DOM4-130-
12 (SEQ ID NO:227), DOM4-130-13 (SEQ ID NO:228), DOM4-130-14 (SEQ ID
NO:229), DOM4-130-15 (SEQ ID NO:230), DOM4-130-16 (SEQ ID NO:231),
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26 (SEQ ID NO:241), DOM4-130-27 (SEQ ID NO:242), DOM4-130-28 (SEQ ID
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NO:250), DOM4-130-38 (SEQ ID NO:251), DOM4-130-39(SEQ ID NO:252),
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42(SEQ ID NO:255), DOM4-130-43(SEQ ID NO:256), DOM4-130-44(SEQ ID
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5 DOM4-130-47 (SEQ ID NO:260), DOM4-130-48 (SEQ ID NO:261), DOM4-130-
49 (SEQ ID NO:262), DOM4-130-50 (SEQ ID NO:263), DOM4-130-51 (SEQ ID
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DOM4-130-54 (SEQ ID NO:267), DOM4-130-55 (SEQ ID NO:268), DOM4-130-
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15 70 (SEQ ID NO:283), DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID
NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287),
DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-
77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID
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DOM4-130-89 (SEQ ID NO:302), DOM4-130-90 (SEQ ID NO:303), DOM4-130-
91 (SEQ ID NO:304), DOM4-130-92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID
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DOM4-130-96 (SEQ ID NO:309), DOM4-130-97 (SEQ ID NO:310), DOM4-130-
98 (SEQ ID NO:311), DOM4-130-99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID
NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315),
DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-
30 130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107
(SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID
NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324),

DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333),
5 DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

In other embodiments, the antagonist of IL-1R1 comprises a dAb that has binding specificity for IL-1R1 and comprises the CDRs of any of the foregoing amino acid sequences.

15

Antibodies and Antibody Portions that Bind a Polypeptide that Enhances Serum Half-Life

As described herein, in some embodiments, the antagonist of IL-1R1 comprises a moiety that binds a polypeptide that enhances serum half-life (e.g.,
20 serum albumin, neonatal Fc receptor). The antibody or antigen-binding fragment that has binding specificity for polypeptide that enhances serum half-life generally has binding specificity for a polypeptide from an animal to which the antagonist of IL-1R1 will be administered. Preferably, the antibody or antigen-binding fragment has binding specificity for human serum albumin or human neonatal Fc receptor.
25 However, veterinary applications are contemplated and the antibody or antigen-binding fragment can have binding specificity for a polypeptide that enhances serum half-life from a desired animal, for example serum albumin from dog, cat, horse, cow, chicken, sheep, pig, goat, deer, mink, and the like. In some embodiments the antibody or antigen-binding fragment has binding specificity for a polypeptide that
30 enhances serum half-life from more than one species. Such antibodies or antigen-binding fragment provide the advantage of allowing preclinical and clinical studies

to be designed and executed using the same antagonist of IL-1R1, and obviate the need to conduct preclinical studies with a suitable surrogate antagonist of IL-1R1.

Suitable antibodies and antigen-binding fragments of antibodies that bind a polypeptide that enhances serum half-life can have the features and properties described in detail herein with respect to antibodies and antigen-binding portions thereof that bind IL-1R1, and can be prepared using any suitable method. For example, antibodies and antigen-binding fragments thereof that bind a polypeptide that enhances serum half-life (*e.g.*, serum albumin, neonatal Fc receptor) be prepared by immunization and/or screening using a selected a polypeptide that enhances serum half-life (*e.g.*, serum albumin, neonatal Fc receptor).

In certain embodiments, the antagonist of IL-1R1 does not contain a mouse, rat and/or rabbit antibody that binds serum albumin or antigen-binding fragment of such an antibody.

The antibody or antigen-binding fragment can bind serum albumin with any desired affinity, on rate and off rate. The affinity (KD), on rate (K_{on} or k_a) and off rate (K_{off} or k_d) can be selected to obtain a desired serum half-life for a particular drug. For example, it may be desirable to obtain a maximal serum half-life for treating a chronic inflammation or a chronic inflammatory disorder, while a shorter half-life may be desirable for a diagnostic applications or for treating acute inflammation or an acute disorder. Generally, a fast on rate and a fast or moderate off rate for binding to serum albumin is preferred. Antagonists of IL-1R1 that comprise an antibody or antigen-binding fragment thereof that binds serum albumin with these characteristics will quickly bind serum albumin after being administered, and will dissociate and rebind serum albumin rapidly. These characteristics will reduce rapid clearance of the antagonist of IL-1R1 (*e.g.*, through the kidneys) but still provide efficient delivery and access to the drug target.

The antigen-binding fragment that binds serum albumin (*e.g.*, dAb) generally binds with a KD of about 1 nM to about 500 μ M. In some embodiments, the antigen-binding fragment binds serum albumin with a KD ($KD=K_{off}(k_d)/K_{on}(k_a)$) of about 10 to about 100 nM, or about 100 nM to about 500 nM, or about 500 nM to about 5 mM, as determined by surface plasmon resonance (*e.g.*, using a BIACORE instrument). In particular embodiments, the drug conjugate, noncovalent drug

conjugate or drug fusion comprises an antigen-binding fragment of an antibody (e.g., a dAb) that binds serum albumin (e.g., human serum albumin) with a K_D of about 50 nM, or about 70 nM, or about 100 nM, or about 150 nM or about 200 nM. The improved pharmacokinetic properties (e.g., prolonged $t_{1/2\beta}$, increased AUC) of drug conjugates, noncovalent drug conjugates and drug fusions described herein may correlate with the affinity of the antigen-binding fragment that binds serum albumin. Accordingly, drug conjugates, noncovalent drug conjugates and drug fusions that have improved pharmacokinetic properties can generally be prepared using an antigen-binding fragment that binds serum albumin (e.g., human serum albumin) with high affinity (e.g., K_D of about 500 nM or less, about 250 nM or less, about 100 nM or less, about 50 nM or less, about 10 nM or less, or about 1 nM or less, or about 100 pM or less).

Preferably, the drug that is conjugated or fused to the antigen-binding fragment that binds serum albumin, binds to its target (the drug target) with an affinity (K_D) that is stronger than the affinity of the antigen-binding fragment for serum albumin and/or a K_{off} (kd) that is faster than the K_{off} of the antigen binding fragment for serum albumin, as measured by surface plasmon resonance (e.g., using a BIACORE instrument). For example, the drug can bind its target with an affinity that is about 1 to about 100000, or about 100 to about 100000, or about 1000 to about 100000, or about 10000 to about 100000 times stronger than the affinity of antigen-binding fragment that binds SA for SA. For example, the antigen-binding fragment of the antibody that binds SA can bind with an affinity of about 10 μ M, while the drug binds its target with an affinity of about 100 pM.

In particular embodiments, the antigen-binding fragment of an antibody that binds serum albumin is a dAb that binds human serum albumin. For example, a V_K dAb having an amino acid sequence selected from the group consisting of DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), and DOM7r-14 (SEQ ID NO:748), or a V_H dAb having an amino acid sequence selected from the group consisting of DOM7h-22 (DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID

NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), and DOM7h-27 (SEQ ID NO:745). In other embodiments, the antigen-binding fragment of an antibody that binds serum albumin is a dAb that binds human serum albumin and comprises the CDRs of any of the foregoing amino acid sequences.

5 In other embodiments, the antigen-binding fragment of an antibody that binds serum albumin is a dAb that binds human serum albumin and comprises an amino acid sequence that has at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with DOM7m-
10 16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1
15 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763),
20 DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776),
25 Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence
30

O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784).

Amino acid sequence identity is preferably determined using a suitable sequence alignment algorithm and default parameters, such as BLAST P (Karlin and
5 Altschul, *Proc. Natl. Acad. Sci. USA* 87(6):2264-2268 (1990)).

Antagonist of IL-1R1 Formats

Antagonist of IL-1R1 moieties (*e.g.*, IL-1ra or a functional variant thereof, dAb) can be formatted into a variety of suitable structures for use in the invention.
10 For example, as described in detail herein, an antagonist of IL-1R1 moiety (*e.g.*, a dAb that binds IL-1R1 and inhibits a function of IL-1R1) can be formatted as a conjugate and protein, polypeptide, and peptide antagonists of IL-1R1 moieties can be formatted as a fusion protein. A protein, polypeptide or peptide antagonist of IL-1R1 (*e.g.*, a dAb that binds IL-1R1 and inhibits a function of IL-1R1) can be
15 formatted as a mono or multispecific antibody or antibody fragment, or into a mono or multispecific non-antibody structure. Suitable formats include, any suitable polypeptide structure in which IL-1ra, a functional variant of IL-1ra, an antibody variable domain or one or more of the CDRs thereof can be incorporated, so as to confer binding specificity for IL-1R1 on the structure. A variety of suitable
20 antibody formats are known in the art, such as, IgG-like formats, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, bispecific antibodies, antibody heavy chains, antibody light chains, homodimers and heterodimers of antibody heavy chains and/or light chains, antigen-binding fragments of any of the foregoing (*e.g.*, a Fv fragment (*e.g.*, single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a F(ab')₂ fragment), a single
25 variable domain (*e.g.*, V_H, V_L, V_{HH}), a dAb, and modified versions of any of the foregoing (*e.g.*, modified by the covalent attachment of polyalkylene glycol (*e.g.*, polyethylene glycol, polypropylene glycol, polybutylene glycol) or other suitable polymer). See, PCT/GB03/002804, filed June 30, 2003, which designated the
30 United States, (WO 2004/081026) regarding PEGylated single variable domains and dAbs, suitable methods for preparing same, increased *in vivo* half life of the PEGylated single variable domains and dAb monomers and multimers, suitable PEGs, preferred hydrodynamic sizes of PEGs, and preferred hydrodynamic sizes of

PEGylated single variable domains and dAb monomers and multimers. The entire teaching of PCT/GB03/002804 (WO 2004/081026), including the portions referred to above, are incorporated herein by reference.

The antagonist of IL-1R1 can be formatted as a dimer, trimer or polymer of a
5 desired dAb monomer that binds IL-1R1, for example, using a suitable linker such as $(\text{Gly}_4\text{Ser})_n$, where n = from 1 to 8, e.g., 1, 2, 3, 4, 5, 6, 7 or 8. If desired, a protein, polypeptide or peptide antagonist of IL-1R1 moiety (including dAb monomers, dimers and trimers, IL-1ra and functional variants thereof) can be linked to an antibody Fc region. For example, a protein, polypeptide or peptide antagonist can
10 be linked to a human IgG (Fc region) comprising one or both of $\text{C}_{\text{H}2}$ and $\text{C}_{\text{H}3}$ domains, and optionally a hinge region, and optionally containing mutations that reduce the ability of the Fc region to fix complement and/or bind Fc receptors. Such mutations are well-known in the art and described, for example, in GB 2,209,757 B (Winter *et al.*), WO 89/07142 (Morrison *et al.*), and WO 94/29351 (Morgan *et al.*), the
15 teachings of these documents with respect to amino acid mutations in Fc regions that reduce Fc receptor binding and/or the ability to fix complement are incorporated herein by reference.

Protein, polypeptide or peptide antagonists of IL-1R1 moieties (e.g., dAb monomers, IL-1ra or functional variants thereof) can also be combined and/or
20 formatted into non-antibody multivalent complexes that comprise two or more copies of the same antagonist of IL-1R1 moiety or two or more different antagonist of IL-1R1 moieties, and which bind cells expressing IL-1R1 with superior avidity. For example natural bacterial receptors such as SpA can be used as scaffolds for the grafting of CDRs to generate non-antibody formats that bind specifically to one
25 or more epitopes of IL-1R1. Details of this procedure are described in US 5,831,012. Other suitable scaffolds include those based on fibronectin and affibodies. Details of suitable procedures are described in WO 98/58965. Other suitable scaffolds include lipocalin and CTLA4, as described in van den Beuken *et al.*, *J. Mol. Biol.* 310:591-601 (2001), and scaffolds such as those described in WO
30 00/69907 (Medical Research Council), which are based for example on the ring structure of bacterial GroEL or other chaperone polypeptides. Protein scaffolds may be combined; for example, CDRs may be grafted on to a CTLA4 scaffold and used

together with immunoglobulin V_H or V_L domains to form an antagonist of IL-1R1 suitable for use in the invention. Likewise, fibronectin, lipocalin and other scaffolds may be combined

5 A variety of suitable methods for preparing any desired format are known in the art. For example, antibody chains and formats (e.g., IgG-like formats, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, bispecific antibodies, antibody heavy chains, antibody light chains, homodimers and heterodimers of antibody heavy chains and/or light chains) can be prepared by expression of suitable expression constructs and/or culture of suitable cells (e.g.,
10 hybridomas, heterohybridomas, recombinant host cells containing recombinant constructs encoding the format). Further, formats such as antigen-binding fragments of antibodies or antibody chains (e.g., a Fv fragment (e.g., single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a F(ab')₂ fragment), can be prepared by expression of suitable expression constructs or by enzymatic digestion
15 of antibodies, for example using papain or pepsin.

A protein, polypeptide or peptide antagonist of IL-1R1 moiety can be formatted as a "dual specific ligand" or a "multispecific ligand," as described in WO 03/002609, the entire teachings of which are incorporated herein by reference. Dual specific ligand comprises immunoglobulin single variable domains that have
20 different binding specificities. Such dual specific ligands can comprise combinations of heavy and light chain domains. For example, the dual specific ligand may comprise a V_H domain and a V_L domain, which may be linked together in the form of an scFv (e.g., using a suitable linker such as Gly₄Ser), or formatted into a bispecific antibody or antigen-binding fragment thereof (e.g. F(ab')₂ fragment).
25 The dual specific ligands do not comprise complementary V_H/V_L pairs which form a conventional two chain antibody antigen-binding site that binds antigen or epitope co-operatively. Instead, the dual format ligands comprise a V_H/V_L complementary pair, wherein the V domains have different binding specificities. A dual specific ligand can comprise one or more C_H or C_L domains if desired. A hinge region
30 domain may also be included if desired. Such combinations of domains may, for example, mimic natural antibodies, such as IgG or IgM, or fragments thereof, such as Fv, scFv, Fab or F(ab')₂ molecules. Other structures, such as a single arm of an

IgG molecule comprising V_H , V_L , C_{H1} and C_L domains, are envisaged. Preferably, the dual specific ligand comprises only two variable domains although several such ligands may be incorporated together into the same protein, for example two such ligands can be incorporated into an IgG or a multimeric immunoglobulin, such as
5 IgM. Alternatively, a plurality of dual specific ligands can be combined to form a multimer. For example, two different dual specific ligands can be combined to create a tetra-specific molecule. It will be appreciated by one skilled in the art that the light and heavy variable regions of a dual-specific ligand can be on the same polypeptide chain, or alternatively, on different polypeptide chains. In the case that
10 the variable regions are on different polypeptide chains, then they may be linked via a linker, generally a flexible linker (such as a polypeptide chain), a chemical linking group, or any other method known in the art.

A multispecific ligand possess more than one epitope binding specificity. Generally, the multi-specific ligand comprises two or more epitope binding
15 domains, such as dAbs or non-antibody protein domain comprising a binding site for an epitope, *e.g.*, an affibody, an SpA domain, an LDL receptor class A domain, an EGF domain, an avimer. Multispecific ligands can be formatted further as described herein.

In some embodiments, the antagonist of IL-1R1 is an IgG-like format. Such
20 formats have the conventional four chain structure of an IgG molecule (2 heavy chains and two light chains), in which one or more of the variable regions (V_H and or V_L) have been replaced with a dAb or single variable domain that has binding specificity for IL-1R1. Preferably, each of the variable regions (2 V_H regions and 2 V_L regions) is replaced with a dAb or single variable domain. The dAb(s) or single
25 variable domain(s) that are included in an IgG-like format can have the same specificity or different specificities. In some embodiments, the IgG-like format is tetravalent and can have one, two, three or four specificities. For example, the IgG-like format can be monospecific and comprises 4 dAbs that have the same specificity (*e.g.*, for the same epitope on IL-1R1); bispecific and comprises 3 dAbs
30 that have the same specificity and another dAb that has a different specificity; bispecific and comprise two dAbs that have the same specificity and two dAbs that have a common but different specificity; trispecific and comprises first and second

dAbs that have the same specificity, a third dAbs with a different specificity and a fourth dAb with a different specificity from the first, second and third dAbs; or tetraspecific and comprise four dAbs that each have a different specificity. Antigen-binding fragments of IgG-like formats (e.g., Fab, F(ab')₂, Fab', Fv, scFv) can be prepared. Preferably, the IgG-like formats or antigen-binding fragments thereof do not crosslink IL-1R1.

Half-life Extended Formats

An antagonist of IL-1R1 or antagonist of IL-1R1 moiety (e.g., dAb monomer, dimer or multimer, dual specific format, multi-specific format) can be formatted to extend its *in vivo* serum half life. Increased *in vivo* half-life is useful in *in vivo* applications of polypeptides, such as immunoglobulins, especially antibodies and most especially antibody fragments of small size such as dAbs. Such fragments (Fvs, disulphide bonded Fvs, Fabs, scFvs, dAbs) are rapidly cleared from the body, which can severely limit clinical applications.

An antagonist of IL-1R1 or antagonist of IL-1R1 moiety can be formatted to have a larger hydrodynamic size, for example, by attachment of a polyalkyleneglycol group (e.g. polyethyleneglycol (PEG) group), serum albumin, transferrin, transferrin receptor or at least the transferrin-binding portion thereof, an antibody Fc region, or by conjugation to an antibody domain. In some embodiments, the antagonist of IL-1R1 (e.g., ligand, dAb monomer) is PEGylated. Preferably the PEGylated antagonist IL-1R1 (e.g., ligand, dAb monomer) binds IL-1R1 with substantially the same affinity as the same antagonist that is not PEGylated. For example, the antagonist of IL-1R1 can be a PEGylated dAb monomer that binds IL-1R1, wherein the PEGylated dAb monomer binds IL-1R1 with an affinity that differs from the affinity of dAb in unPEGylated form by no more than a factor of about 1000, preferably no more than a factor of about 100, more preferably no more than a factor of about 10, or with affinity substantially unchanged relative to the unPEGylated form.

Examples of suitable albumin, albumin fragments or albumin variants for use in antagonists of IL-1R1 are described in WO 2005/077042A2, which is

incorporated herein by reference in its entirety. In particular, the following albumin, albumin fragments or albumin variants can be used in the present invention:

- SEQ ID NO:1 (as disclosed in WO 2005/077042A2, this sequence being explicitly incorporated into the present disclosure by reference);
- 5 • Albumin fragment or variant comprising or consisting of amino acids 1-387 of SEQ ID NO:1 in WO 2005/077042A2;
- Albumin, or fragment or variant thereof, comprising an amino acid sequence selected from the group consisting of: (a) amino acids 54 to 61 of SEQ ID NO:1 in WO 2005/077042A2; (b) amino acids 76 to 89 of SEQ ID NO:1 in WO 2005/077042A2; (c) amino acids 92 to 100 of SEQ ID NO:1 in WO 2005/077042A2; (d) amino acids 170 to 176 of SEQ ID NO:1 in WO 2005/077042A2; (e) amino acids 247 to 252 of SEQ ID NO:1 in WO 2005/077042A2; (f) amino acids 266 to 277 of SEQ ID NO:1 in WO 2005/077042A2; (g) amino acids 280 to 288 of SEQ ID NO:1 in WO 2005/077042A2; (h) amino acids 362 to 368 of SEQ ID NO:1 in WO 2005/077042A2; (i) amino acids 439 to 447 of SEQ ID NO:1 in WO 2005/077042A2 (j) amino acids 462 to 475 of SEQ ID NO:1 in WO 2005/077042A2; (k) amino acids 478 to 486 of SEQ ID NO:1 in WO 2005/077042A2; and (l) amino acids 560 to 566 of SEQ ID NO:1 in WO 2005/077042A2.

Further examples of suitable albumin, fragments and analogs for use in an antagonist of IL-1R1 according to the invention are described in WO 03/076567A2, which is incorporated herein by reference in its entirety. In particular, the following albumin, fragments or variants can be used in the present invention:

- 25 • Human serum albumin as described in WO 03/076567A2, eg, in figure 3 (this sequence information being explicitly incorporated into the present disclosure by reference);
- Human serum albumin (HA) consisting of a single non-glycosylated polypeptide chain of 585 amino acids with a formula molecular weight of 66,500 (See, Meloun, *et al.*, *FEBS Letters* 58:136 (1975); Behrens, *et al.*,
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Fed. Proc. 34:591 (1975); Lawn, *et al.*, *Nucleic Acids Research* 9:6102-6114 (1981); Minghetti, *et al.*, *J. Biol. Chem.* 261:6747 (1986));

- A polymorphic variant or analog or fragment of albumin as described in Weitkamp, *et al.*, *Ann. Hum. Genet.* 37:219 (1973);
- 5 • An albumin fragment or variant as described in EP 322094, eg, HA(1-373., HA(1-388), HA(1-389), HA(1-369), and HA(1-419) and fragments between 1-369 and 1-419;
- An albumin fragment or variant as described in EP 399666, eg, HA(1-177) and HA(1-200) and fragments between HA(1-X), where X is any number
10 from 178 to 199.

Where a (one or more) half-life extending moiety (e.g., albumin, transferrin and fragments and analogues thereof) is used in the antagonist of IL-1R1, it can be conjugated using any suitable method, such as, by direct fusion to an antagonist of IL-1R1 moiety, for example by using a single nucleotide construct that encodes a
15 fusion protein, wherein the fusion protein is encoded as a single polypeptide chain with the half-life extending moiety located N- or C-terminally to the antagonist of IL-1R1 moiety. Alternatively, conjugation can be achieved by using a peptide linker between moieties, e.g., a peptide linker as described in WO 03/076567A2 or WO 2004/003019 (these linker disclosures being incorporated by reference in the present
20 disclosure to provide examples for use in the present invention).

Small antagonists of IL-1R1 or antagonist of IL-1R1 moieties, such as a dAb monomer, can be formatted as a larger antigen-binding fragment of an antibody or as and antibody (e.g., formatted as a Fab, Fab', F(ab)₂, F(ab')₂, IgG, scFv). The hydrodynamic size of an antagonist of IL-1R1 (e.g., dAb monomer) and its serum
25 half-life can also be increased by conjugating or linking the antagonist of IL-1R1 to a binding domain (e.g., antibody or antibody fragment) that binds an antigen or epitope that increases half-live *in vivo*, as described herein. For example, the antagonist of IL-1R1 (e.g., dAb monomer) can be conjugated or linked to an anti-serum albumin or anti-neonatal Fc receptor antibody or antibody fragment, e.g. an
30 anti-SA or anti-neonatal Fc receptor dAb, Fab, Fab' or scFv, or to an anti-SA affibody or anti-neonatal Fc receptor affibody.

Typically, a polypeptide that enhances serum half-life *in vivo* is a polypeptide which occurs naturally *in vivo* and which resists degradation or removal by endogenous mechanisms which remove unwanted material from the organism (*e.g.*, human). For example, a polypeptide that enhances serum half-life *in vivo* can be
5 selected from proteins from the extracellular matrix, proteins found in blood, proteins found at the blood brain barrier or in neural tissue, proteins localized to the kidney, liver, lung, heart, skin or bone, stress proteins, disease-specific proteins, or proteins involved in Fc transport.

Suitable polypeptides that enhance serum half-life *in vivo* include, for
10 example, transferrin receptor specific ligand-neuropharmaceutical agent fusion proteins (see U.S. Patent No. 5,977,307, the teachings of which are incorporated herein by reference), brain capillary endothelial cell receptor, transferrin, transferrin receptor (*e.g.*, soluble transferrin receptor), insulin, insulin-like growth factor 1 (IGF 1) receptor, insulin-like growth factor 2 (IGF 2) receptor, insulin receptor, blood
15 coagulation factor X, α 1-antitrypsin and HNF 1 α . Suitable polypeptides that enhance serum half-life also include alpha-1 glycoprotein (orosomucoid; AAG), alpha-1 antichymotrypsin (ACT), alpha-1 microglobulin (protein HC; AIM), antithrombin III (AT III), apolipoprotein A-1 (Apo A-1), apolipoprotein B (Apo B), ceruloplasmin (Cp), complement component C3 (C3), complement component C4
20 (C4), C1 esterase inhibitor (C1 INH), C-reactive protein (CRP), ferritin (FER), hemopexin (HPX), lipoprotein(a) (Lp(a)), mannose-binding protein (MBP), myoglobin (Myo), prealbumin (transthyretin; PAL), retinol-binding protein (RBP), and rheumatoid factor (RF).

Suitable proteins from the extracellular matrix include, for example,
25 collagens, laminins, integrins and fibronectin. Collagens are the major proteins of the extracellular matrix. About 15 types of collagen molecules are currently known, found in different parts of the body, *e.g.* type I collagen (accounting for 90% of body collagen) found in bone, skin, tendon, ligaments, cornea, internal organs or type II collagen found in cartilage, vertebral disc, notochord, and vitreous humor of the eye.

30 Suitable proteins from the blood include, for example, plasma proteins (*e.g.*, fibrin, α -2 macroglobulin, serum albumin, fibrinogen (*e.g.*, fibrinogen A, fibrinogen B), serum amyloid protein A, haptoglobin, profilin, ubiquitin, uteroglobulin and β -2-

microglobulin), enzymes and enzyme inhibitors (*e.g.*, plasminogen, lysozyme, cystatin C, alpha-1-antitrypsin and pancreatic trypsin inhibitor), proteins of the immune system, such as immunoglobulin proteins (*e.g.*, IgA, IgD, IgE, IgG, IgM, immunoglobulin light chains (kappa/lambda)), transport proteins (*e.g.*, retinol binding protein, α -1 microglobulin), defensins (*e.g.*, beta-defensin 1, neutrophil defensin 1, neutrophil defensin 2 and neutrophil defensin 3) and the like.

Suitable proteins found at the blood brain barrier or in neural tissue include, for example, melanocortin receptor, myelin, ascorbate transporter and the like.

Suitable polypeptides that enhances serum half-life *in vivo* also include proteins localized to the kidney (*e.g.*, polycystin, type IV collagen, organic anion transporter Kl, Heymann's antigen), proteins localized to the liver (*e.g.*, alcohol dehydrogenase, G250), proteins localized to the lung (*e.g.*, secretory component, which binds IgA), proteins localized to the heart (*e.g.*, HSP 27, which is associated with dilated cardiomyopathy), proteins localized to the skin (*e.g.*, keratin), bone specific proteins such as morphogenic proteins (BMPs), which are a subset of the transforming growth factor β superfamily of proteins that demonstrate osteogenic activity (*e.g.*, BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8), tumor specific proteins (*e.g.*, trophoblast antigen, herceptin receptor, oestrogen receptor, cathepsins (*e.g.*, cathepsin B, which can be found in liver and spleen)).

Suitable disease-specific proteins include, for example, antigens expressed only on activated T-cells, including LAG-3 (lymphocyte activation gene), osteoprotegerin ligand (OPGL; see *Nature* 402, 304-309 (1999)), OX40 (a member of the TNF receptor family, expressed on activated T cells and specifically up-regulated in human T cell leukemia virus type-I (HTLV-I)-producing cells; see *Immunol.* 165 (1):263-70 (2000)). Suitable disease-specific proteins also include, for example, metalloproteases (associated with arthritis/cancers) including CG6512 *Drosophila*, human paraplegin, human FtsH, human AFG3L2, murine ftsH; and angiogenic growth factors, including acidic fibroblast growth factor (FGF-1), basic fibroblast growth factor (FGF-2), vascular endothelial growth factor/vascular permeability factor (VEGF/VPF), transforming growth factor- α (TGF α), tumor necrosis factor-alpha (TNF- α), angiogenin, interleukin-3 (IL-3), interleukin-8 (IL-

8), platelet-derived endothelial growth factor (PD-ECGF), placental growth factor (PlGF), midkine platelet-derived growth factor-BB (PDGF), and fractalkine.

Suitable polypeptides that enhance serum half-life *in vivo* also include stress proteins such as heat shock proteins (HSPs). HSPs are normally found intracellularly. When they are found extracellularly, it is an indicator that a cell has died and spilled out its contents. This unprogrammed cell death (necrosis) occurs when as a result of trauma, disease or injury, extracellular HSPs trigger a response from the immune system. Binding to extracellular HSP can result in localizing the compositions of the invention to a disease site.

Suitable proteins involved in Fc transport include, for example, Brambell receptor (also known as FcRB). This Fc receptor has two functions, both of which are potentially useful for delivery. The functions are (1) transport of IgG from mother to child across the placenta (2) protection of IgG from degradation thereby prolonging its serum half-life. It is thought that the receptor recycles IgG from endosomes. (See, Holliger *et al*, *Nat Biotechnol* 15(7):632-6 (1997).)

Methods for pharmacokinetic analysis and determination of half-life will be familiar to those skilled in the art. Details may be found in *Kenneth, A et al*: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in *Peters et al*, Pharmacokinetic analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd Rev. ex edition (1982), which describes pharmacokinetic parameters such as t alpha and t beta half lives and area under the curve (AUC).

Particular examples of half-life extended formats are described further below.

Antagonist of IL-1R1 Fusion Proteins

Antagonist of IL-1R1 fusion proteins suitable for use in the invention are fusion proteins that comprise a continuous polypeptide chain, said chain comprising an antigen-binding fragment of an antibody that binds a polypeptide that extends serum half-life (e.g., serum albumin) as a first moiety, linked to a second moiety (antagonist of IL-1R1 moiety) that is a polypeptide antagonist of IL-1R1. The first and second moieties can be directly bonded to each other through a peptide bond, or

linked through a suitable amino acid, or peptide or polypeptide linker. Additional moieties (*e.g.*, third, fourth) and/or linker sequences can be present as appropriate. The first moiety can be in an N-terminal location, C-terminal location or internal relative to the second moiety (*i.e.*, the polypeptide antagonist of IL-1R1). The

5 moieties can occur on the continuous polypeptide chain in any desired order. In certain embodiments, each moiety can be present in more than one copy. For example, the antagonist of IL-1R1 fusion can comprise two or more first moieties each comprising an antigen-binding fragment of an antibody that binds a polypeptide that enhances serum half-life (*e.g.*, a V_H that binds human serum

10 albumin and a V_L that bind human serum albumin or two or more V_{HS} or V_{LS} that bind human serum albumin).

In certain embodiments, the fusion protein is a continuous polypeptide chain that has the formula (amino-terminal to carboxy-terminal):

15 a-(P)_{n2}-b-(X)_{n1}-c-(Q)_{n3}-d or a-(Q)_{n3}-b-(X)_{n1}-c-(P)_{n2}-d

wherein X is a polypeptide antagonist of IL-1R1 moiety;

P and Q are each independently a polypeptide binding moiety that contains a binding site that has binding specificity for a polypeptide that enhances serum half-

20 life *in vivo*;

a, b, c and d are each independently absent or one to about 100 amino acid residues;

n₁, n₂ and n₃ represent the number of X, P or Q moieties present, respectively;

25 n₁ is one to about 10;
 n₂ is zero to about 10; and
 n₃ is zero to about 10,

with the proviso that both n₂ and n₃ are not zero.

In some embodiments, when n₁ and n₂ are both one and n₃ is zero, X does

30 not comprise an antibody chain or a fragment of an antibody chain.

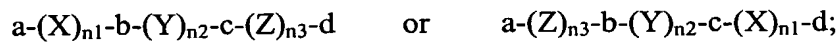
In some embodiments, n_2 is one, two, three, four, five or six, and n_3 is zero. In other embodiments, n_3 is one, two, three, four, five or six, and n_2 is zero. In other embodiments, n_1 , n_2 and n_3 are each one.

In certain embodiments, X does not comprises an antibody chain or a
5 fragment of an antibody chain.

In preferred embodiments, P and Q are each independently a polypeptide binding moiety that has binding specificity for serum albumin.

In some embodiments, the antagonist of IL-1R1 fusion protein is a continuous polypeptide chain that has the formula:

10



wherein X is a polypeptide that has binding specificity for IL-1R1;

Y is a single chain antigen-binding fragment of an antibody that has binding
15 specificity for serum albumin;

Z is a polypeptide drug that has binding specificity for a second target;

a, b, c and d are each independently absent or one to about 100 amino acid residues;

n_1 is one to about 10;

20 n_2 is one to about 10; and

n_3 is zero to about 10.

In some embodiments, when n_1 and n_2 are both one and n_3 is zero, X does not comprise an antibody chain or a fragment of an antibody chain.

In one embodiment, neither X nor Z comprises an antibody chain or a
25 fragment of an antibody chain. In one embodiment, n_1 is one, n_3 is one and n_2 is two, three, four, five, six, seven, eight or nine. Preferably, Y is an immunoglobulin heavy chain variable domain (V_H , V_{HH}) that has binding specificity for serum albumin, or an immunoglobulin light chain variable domain (V_L) that has binding specificity for serum albumin. More preferably, Y is a dAb (*e.g.*, a V_H , V_Λ) that
30 binds human serum albumin. In a particular embodiment, X or Z is human IL-1ra or a functional variant of human IL-1ra.

In certain embodiments, Y comprises an amino acid sequence selected from the group consisting of DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), and DOM7r-14 (SEQ ID NO:748). In other embodiments, Y
5 comprises an amino acid sequence selected from the group consisting of DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), and DOM7h-27 (SEQ ID NO:745).

10 In certain embodiments, X and Z are independently a binding domain that has a binding site with binding specificity for IL-1R1. In some embodiments X and/or Z independently comprise an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7),
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(SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID
25 NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343),
DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-
130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID
NO:348), and DOM4-133 (SEQ ID NO:349).

In other embodiments, the drug fusion comprises moieties X' and Y',
30 wherein X' is a polypeptide antagonist of IL-1R1, with the proviso that X' does not
comprise an antibody chain or a fragment of an antibody chain; and Y' is a single
chain antigen-binding fragment of an antibody that has binding specificity for serum

albumin. Preferably, Y' is an immunoglobulin heavy chain variable domain (V_H, V_{HH}) that has binding specificity for serum albumin, or an immunoglobulin light chain variable domain (V_L) that has binding specificity for serum albumin. More preferably, Y' is a dAb (e.g., a V_H, V_κ or V_λ) that binds human serum albumin. X' can be located amino terminally to Y', or Y' can be located amino terminally to X'. In some embodiments, X' and Y' are separated by an amino acid, or by a peptide or polypeptide linker that comprises from two to about 100 amino acids. In a particular embodiment, X' is human IL-1ra or a functional variant of human IL-1ra.

In other embodiments, X' is a binding domain that has a binding site with binding specificity for IL-1R1. In particular embodiments the antagonist of IL-1R1 fusion comprises a dAb that binds serum albumin and human IL-1ra (e.g., SEQ ID NO:786). Preferably, the dAb binds human serum albumin and comprises human framework regions. In some embodiments, X' comprise an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ

ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113 (SEQ ID NO:86), DOM4-114 (SEQ ID NO:87), DOM4-115 (SEQ ID NO:88), DOM4-116 (SEQ ID NO:89), DOM4-117 (SEQ ID NO:90), DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102), DOM4-122-8 (SEQ ID NO:103), DOM4-122-9 (SEQ ID NO:104), DOM4-122-10 (SEQ ID NO:105), DOM4-122-11 (SEQ ID NO:106), DOM4-122-12 (SEQ ID NO:107), DOM4-122-13 (SEQ ID NO:108), DOM4-122-14 (SEQ ID NO:109), DOM4-122-15 (SEQ ID NO:110), DOM4-122-16 (SEQ ID NO:111), DOM4-122-17 (SEQ ID NO:112), DOM4-122-18 (SEQ ID NO:113), DOM4-122-19 (SEQ ID NO:114), DOM4-122-20 (SEQ ID NO:115), DOM4-122-21 (SEQ ID NO:116), DOM4-122-22 (SEQ ID NO:117), DOM4-122-25 (SEQ ID NO:118), DOM4-122-26 (SEQ ID NO:119), DOM4-122-27 (SEQ ID NO:120), DOM4-122-28 (SEQ ID NO:121), DOM4-122-29 (SEQ ID NO:122), DOM4-122-30 (SEQ ID NO:123), DOM4-122-31 (SEQ ID NO:124), DOM4-122-32 (SEQ ID NO:125), DOM4-122-33 (SEQ ID NO:126), DOM4-122-34 (SEQ ID NO:127), DOM4-122-35 (SEQ ID NO:128), DOM4-122-36 (SEQ ID NO:129), DOM4-122-37 (SEQ ID NO:130), DOM4-122-38 (SEQ ID NO:131), DOM4-122-39 (SEQ ID NO:132), DOM4-122-40 (SEQ ID NO:133),

DOM4-122-41 (SEQ ID NO:134), DOM4-122-42 (SEQ ID NO:135), DOM4-122-43 (SEQ ID NO:136), DOM4-122-44 (SEQ ID NO:137), DOM4-122-45 (SEQ ID NO:138), DOM4-122-46 (SEQ ID NO:139), DOM4-122-47 (SEQ ID NO:140), DOM4-122-48 (SEQ ID NO:141), DOM4-122-49 (SEQ ID NO:142), DOM4-122-50 (SEQ ID NO:143), DOM4-122-51 (SEQ ID NO:144), DOM4-122-52 (SEQ ID NO:145), DOM4-122-54 (SEQ ID NO:146), DOM4-122-55 (SEQ ID NO:147), DOM4-122-56 (SEQ ID NO:148), DOM4-122-57 (SEQ ID NO:149), DOM4-122-58 (SEQ ID NO:150), DOM4-122-59 (SEQ ID NO:151), DOM4-122-60 (SEQ ID NO:152), DOM4-122-61 (SEQ ID NO:153), DOM4-122-62 (SEQ ID NO:154), DOM4-122-63 (SEQ ID NO:155), DOM4-122-64 (SEQ ID NO:156), DOM4-122-65 (SEQ ID NO:157), DOM4-122-66 (SEQ ID NO:158), DOM4-122-67 (SEQ ID NO:159), DOM4-122-68 (SEQ ID NO:160), DOM4-122-69 (SEQ ID NO:161), DOM4-122-70 (SEQ ID NO:162), DOM4-122-71 (SEQ ID NO:163), DOM4-122-72 (SEQ ID NO:164), DOM4-122-73 (SEQ ID NO:165), DOM4-123 (SEQ ID NO:166), DOM4-124 (SEQ ID NO:167) DOM4-125 (SEQ ID NO:168), DOM4-126 (SEQ ID NO:169), DOM4-127 (SEQ ID NO:170), DOM4-128 (SEQ ID NO:171), DOM4-129 (SEQ ID NO:172), DOM4-129-1 (SEQ ID NO:173,) DOM4-129-2 (SEQ ID NO:174), DOM4-129-3 (SEQ ID NO:175), DOM4-129-4 (SEQ ID NO:176), DOM4-129-5 (SEQ ID NO:177), DOM4-129-6 (SEQ ID NO:178), DOM4-129-7 (SEQ ID NO:179), DOM4-129-8 (SEQ ID NO:180), DOM4-129-9 (SEQ ID NO:181), DOM4-129-10 (SEQ ID NO:182), DOM4-129-11 (SEQ ID NO:183), DOM4-129-12 (SEQ ID NO:184), DOM4-129-13 (SEQ ID NO:185), DOM4-129-14 (SEQ ID NO:186), DOM4-129-15 (SEQ ID NO:187), DOM4-129-16 (SEQ ID NO:188), DOM4-129-17 (SEQ ID NO:189), DOM4-129-18 (SEQ ID NO:190), DOM4-129-19 (SEQ ID NO:191), DOM4-129-20 (SEQ ID NO:192), DOM4-129-21 (SEQ ID NO:193), DOM4-129-22 (SEQ ID NO:194), DOM4-129-23 (SEQ ID NO:195), DOM4-129-24 (SEQ ID NO:196), DOM4-129-25 (SEQ ID NO:197), DOM4-129-26 (SEQ ID NO:198), DOM4-129-27 (SEQ ID NO:199), DOM4-129-28 (SEQ ID NO:200), DOM4-129-29 (SEQ ID NO:201), DOM4-129-31 (SEQ ID NO:202), DOM4-129-32 (SEQ ID NO:203), DOM4-129-33 (SEQ ID NO:204), DOM4-129-34 (SEQ ID NO:205), DOM4-129-35 (SEQ ID NO:206), DOM4-129-37 (SEQ ID NO:207), DOM4-129-38 (SEQ ID NO:208), DOM4-129-

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DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287), DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID NO:292), DOM4-130-80 (SEQ ID NO:293), DOM4-130-81 (SEQ ID NO:294), DOM4-130-82 (SEQ ID NO:295), DOM4-130-83 (SEQ ID NO:296), DOM4-130-84 (SEQ ID NO:297), DOM4-130-85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID NO:300), DOM4-130-88 (SEQ ID NO:301), DOM4-130-89 (SEQ ID NO:302), DOM4-130-90 (SEQ ID NO:303), DOM4-130-91 (SEQ ID NO:304), DOM4-130-92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID NO:307), DOM4-130-95 (SEQ ID NO:308), DOM4-130-96 (SEQ ID NO:309), DOM4-130-97 (SEQ ID NO:310), DOM4-130-98 (SEQ ID NO:311), DOM4-130-99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315), DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107 (SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324), DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

In certain embodiments, Y' comprises an amino acid sequence selected from the group consisting of DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID

NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), and DOM7r-14 (SEQ ID NO:748). In other embodiments, Y' comprises an amino acid sequence selected from the group consisting of DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741),
 5 DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), and DOM7h-27 (SEQ ID NO:745).

In other embodiments, the antagonist of IL-1R1 fusion or IL-1R1 conjugate comprises a functional variant of human IL-1ra that has at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 96%,
 10 or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with the mature 152 amino acid form of human IL-1ra and antagonizes human Interleukin-1 type 1 receptor. (See, Eisenberg *et al.*, *Nature* 343:341-346 (1990).) The IL-1ra variant can comprise one or more additional amino acids (*e.g.*, comprise 153 or 154 or more amino acids).

15 In other embodiments, the antagonist of IL-1R1 fusion or IL-1R1 conjugate comprises a dAb that binds human IL-1R1 and inhibits a function of human IL-1 R1, and has an amino acid sequence that has at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence
 20 identity with the amino acid sequence of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32),
 30 DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35).

NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46),

5 DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60),

10 DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74),

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20 DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102), DOM4-122-8 (SEQ ID NO:103), DOM4-122-9 (SEQ ID NO:104), DOM4-122-10 (SEQ ID NO:105),

25 DOM4-122-11 (SEQ ID NO:106), DOM4-122-12 (SEQ ID NO:107), DOM4-122-13 (SEQ ID NO:108), DOM4-122-14 (SEQ ID NO:109), DOM4-122-15 (SEQ ID NO:110), DOM4-122-16 (SEQ ID NO:111), DOM4-122-17 (SEQ ID NO:112),

30 DOM4-122-18 (SEQ ID NO:113), DOM4-122-19 (SEQ ID NO:114), DOM4-122-20 (SEQ ID NO:115), DOM4-122-21 (SEQ ID NO:116), DOM4-122-22 (SEQ ID NO:117), DOM4-122-25 (SEQ ID NO:118), DOM4-122-26 (SEQ ID NO:119),

DOM4-122-27 (SEQ ID NO:120), DOM4-122-28 (SEQ ID NO:121), DOM4-122-29 (SEQ ID NO:122), DOM4-122-30 (SEQ ID NO:123), DOM4-122-31 (SEQ ID NO:124), DOM4-122-32 (SEQ ID NO:125), DOM4-122-33 (SEQ ID NO:126), DOM4-122-34 (SEQ ID NO:127), DOM4-122-35 (SEQ ID NO:128), DOM4-122-36 (SEQ ID NO:129), DOM4-122-37 (SEQ ID NO:130), DOM4-122-38 (SEQ ID NO:131), DOM4-122-39 (SEQ ID NO:132), DOM4-122-40 (SEQ ID NO:133), DOM4-122-41 (SEQ ID NO:134), DOM4-122-42 (SEQ ID NO:135), DOM4-122-43 (SEQ ID NO:136), DOM4-122-44 (SEQ ID NO:137), DOM4-122-45 (SEQ ID NO:138), DOM4-122-46 (SEQ ID NO:139), DOM4-122-47 (SEQ ID NO:140), DOM4-122-48 (SEQ ID NO:141), DOM4-122-49 (SEQ ID NO:142), DOM4-122-50 (SEQ ID NO:143), DOM4-122-51 (SEQ ID NO:144), DOM4-122-52 (SEQ ID NO:145), DOM4-122-54 (SEQ ID NO:146), DOM4-122-55 (SEQ ID NO:147), DOM4-122-56 (SEQ ID NO:148), DOM4-122-57 (SEQ ID NO:149), DOM4-122-58 (SEQ ID NO:150), DOM4-122-59 (SEQ ID NO:151), DOM4-122-60 (SEQ ID NO:152), DOM4-122-61 (SEQ ID NO:153), DOM4-122-62 (SEQ ID NO:154), DOM4-122-63 (SEQ ID NO:155), DOM4-122-64 (SEQ ID NO:156), DOM4-122-65 (SEQ ID NO:157), DOM4-122-66 (SEQ ID NO:158), DOM4-122-67 (SEQ ID NO:159), DOM4-122-68 (SEQ ID NO:160), DOM4-122-69 (SEQ ID NO:161), DOM4-122-70 (SEQ ID NO:162), DOM4-122-71 (SEQ ID NO:163), DOM4-122-72 (SEQ ID NO:164), DOM4-122-73 (SEQ ID NO:165), DOM4-123 (SEQ ID NO:166), DOM4-124 (SEQ ID NO:167), DOM4-125 (SEQ ID NO:168), DOM4-126 (SEQ ID NO:169), DOM4-127 (SEQ ID NO:170), DOM4-128 (SEQ ID NO:171), DOM4-129 (SEQ ID NO:172), DOM4-129-1 (SEQ ID NO:173), DOM4-129-2 (SEQ ID NO:174), DOM4-129-3 (SEQ ID NO:175), DOM4-129-4 (SEQ ID NO:176), DOM4-129-5 (SEQ ID NO:177), DOM4-129-6 (SEQ ID NO:178), DOM4-129-7 (SEQ ID NO:179), DOM4-129-8 (SEQ ID NO:180), DOM4-129-9 (SEQ ID NO:181), DOM4-129-10 (SEQ ID NO:182), DOM4-129-11 (SEQ ID NO:183), DOM4-129-12 (SEQ ID NO:184), DOM4-129-13 (SEQ ID NO:185), DOM4-129-14 (SEQ ID NO:186), DOM4-129-15 (SEQ ID NO:187), DOM4-129-16 (SEQ ID NO:188), DOM4-129-17 (SEQ ID NO:189), DOM4-129-18 (SEQ ID NO:190), DOM4-129-19 (SEQ ID NO:191), DOM4-129-20 (SEQ ID NO:192), DOM4-129-21 (SEQ ID NO:193), DOM4-129-22 (SEQ ID NO:194), DOM4-129-

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(SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

5 The antagonist of IL-1R1 fusions of the invention can be produced using any suitable method. For example, some embodiments can be produced by the insertion of a nucleic acid encoding the antagonist of IL-1R1 fusion into a suitable expression vector. The resulting construct can be introduced into a suitable host cell for expression. Upon expression, fusion protein can be isolated or purified from a cell lysate or preferably from the culture media or periplasm using any suitable method.
10 (See *e.g.*, *Current Protocols in Molecular Biology* (Ausubel, F.M. *et al.*, eds., Vol. 2, Suppl. 26, pp. 16.4.1-16.7.8 (1991))).

Suitable expression vectors can contain a number of components, for example, an origin of replication, a selectable marker gene, one or more expression control elements, such as a transcription control element (*e.g.*, promoter, enhancer,
15 terminator) and/or one or more translation signals, a signal sequence or leader sequence, and the like. Expression control elements and a signal sequence, if present, can be provided by the vector or other source. For example, the transcriptional and/or translational control sequences of a cloned nucleic acid encoding an antibody chain can be used to direct expression.

20 A promoter can be provided for expression in a desired host cell. Promoters can be constitutive or inducible. For example, a promoter can be operably linked to a nucleic acid encoding an antibody, antibody chain or portion thereof, such that it directs transcription of the nucleic acid. A variety of suitable promoters for procaryotic (*e.g.*, lac, tac, T3, T7 promoters for *E. coli*) and eucaryotic (*e.g.*, simian
25 virus 40 early or late promoter, Rous sarcoma virus long terminal repeat promoter, cytomegalovirus promoter, adenovirus late promoter) hosts are available.

In addition, expression vectors typically comprise a selectable marker for selection of host cells carrying the vector, and, in the case of a replicable expression vector, an origin or replication. Genes encoding products which confer antibiotic or
30 drug resistance are common selectable markers and may be used in procaryotic (*e.g.*, lactamase gene (ampicillin resistance), *Tet* gene for tetracycline resistance) and eucaryotic cells (*e.g.*, neomycin (G418 or geneticin), gpt (mycophenolic acid),

ampicillin, or hygromycin resistance genes). Dihydrofolate reductase marker genes permit selection with methotrexate in a variety of hosts. Genes encoding the gene product of auxotrophic markers of the host (*e.g.*, *LEU2*, *URA3*, *HIS3*) are often used as selectable markers in yeast. Use of viral (*e.g.*, baculovirus) or phage vectors, and
5 vectors which are capable of integrating into the genome of the host cell, such as retroviral vectors, are also contemplated. Suitable expression vectors for expression in mammalian cells and prokaryotic cells (*E. coli*), insect cells (*Drosophila* Schnieder S2 cells, Sf9) and yeast (*P. methanolica*, *P. pastoris*, *S. cerevisiae*) are well-known in the art.

10 Antagonist of IL-1R1 fusions can be produced by the expression of a recombinant nucleic acid encoding the protein (*e.g.*, an expression vector) in a suitable host cell, or using other suitable methods. For example, the expression constructs described herein can be introduced into a suitable host cell, and the resulting cell can be maintained (*e.g.*, in culture, in an animal) under conditions
15 suitable for expression of the constructs. The antagonist of IL-1R1 fusion can be isolated (*e.g.*, from the culture media) if desired. Suitable host cells can be prokaryotic, including bacterial cells such as *E. coli*, *B. subtilis* and or other suitable bacteria, eucaryotic, such as fungal or yeast cells (*e.g.*, *Pichia pastoris*, *Aspergillus species*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Neurospora*
20 *crassa*), or other lower eucaryotic cells, and cells of higher eucaryotes such as those from insects (*e.g.*, Sf9 insect cells (WO 94/26087 (O'Connor)) or mammals (*e.g.*, COS cells, such as COS-1 (ATCC Accession No. CRL-1650) and COS-7 (ATCC Accession No. CRL-1651), CHO (*e.g.*, ATCC Accession No. CRL-9096) , 293
(ATCC Accession No. CRL-1573), HeLa (ATCC Accession No. CCL-2), CV1
25 (ATCC Accession No. CCL-70), WOP (Dailey *et al.*, *J. Virol.* 54:739-749 (1985)), 3T3, 293T (Pear *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 90:8392-8396 (1993)), NSO cells, SP2/0, HuT 78 cells, and the like (see, *e.g.*, Ausubel, F.M. *et al.*, eds. *Current Protocols in Molecular Biology*, Greene Publishing Associates and John Wiley & Sons Inc., (1993)).

30 Antagonist of IL-1R1 Conjugates

In another aspect, the invention provides conjugates comprising an antigen-binding fragment of an antibody that binds serum albumin that is bonded to an antagonist of IL-1R1. Such conjugates include “antagonist of IL-1R1 conjugates,” which comprise an antigen-binding fragment of an antibody that binds serum albumin to which an antagonist of IL-1R1 is covalently bonded, and “noncovalent antagonist of IL-1R1 conjugates,” which comprise an antigen-binding fragment of an antibody that binds serum albumin to which an antagonist of IL-1R1 is noncovalently bonded. Preferably, the conjugates are sufficiently stable so that the antigen-binding fragment of an antibody that binds serum albumin and antagonist of IL-1R1 remain substantially bonded (either covalently or noncovalently) to each other under *in vivo* conditions (*e.g.*, when administered to a human). Preferably, no more than about 20%, no more than about 15%, no more than about 10%, no more than about 9%, no more than about 8%, no more than about 7%, no more than about 6%, no more than about 5%, no more than about 4%, no more than about 3%, no more than about 2%, no more than about 1% or substantially none of the conjugates dissociate or break down to release drug and antigen-binding fragment under *in vivo* conditions. For example, stability under “*in vivo*” conditions can be conveniently assessed by incubating drug conjugate or noncovalent drug conjugate for 24 hours in serum (*e.g.*, human serum) at 37°C. In one example of such a method, equal amounts of a drug conjugate and the unconjugated drug are diluted into two different vials of serum. Half of the contents of each vial is immediately frozen at -20°C, and the other half incubated for 24 hours at 37°C. All four samples can then be analyzed using any suitable method, such as SDS-PAGE and/or Western blotting. Western blots can be probed using an antibody that binds the drug. All drug in the drug conjugate lanes will run at the size of the drug conjugate if there was no dissociation. Many other suitable methods can be used to assess stability under “*in vivo*” conditions, for example, by analyzing samples prepared as described above using suitable analytic methods, such as chromatography (*e.g.*, gel filtration, ion exchange, reversed phase), ELISA, mass spectroscopy and the like.

30

Covalent Antagonist of IL-1R1 Conjugates

In another aspect, the invention provides an antagonist of IL-1R1 conjugate comprising an antigen-binding fragment of an antibody that has binding specificity for serum albumin, and an antagonist of IL-1R1 that is covalently bonded to said antigen-binding fragment, with the proviso that the antagonist of IL-1R1 conjugate
5 is not a single continuous polypeptide chain.

In some embodiments, the antagonist of IL-1R1 conjugate comprises an immunoglobulin heavy chain variable domain (V_H , V_{HH}) that has binding specificity for serum albumin, or an immunoglobulin light chain variable domain (V_L) that has binding specificity for serum albumin, and an antagonist of IL-1R1 moiety that is
10 covalently bonded to said V_H or V_L , with the proviso that the antagonist of IL-1R1 conjugate is not a single continuous polypeptide chain. Preferably the antagonist of IL-1R1 conjugate comprises a single V_H that binds serum albumin or a single V_L that binds serum albumin. In certain embodiments, the antagonist of IL-1R1 conjugate comprises a V_k dAb that binds human serum albumin and comprises an
15 amino acid sequence selected from the group consisting of DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), and DOM7r-14 (SEQ ID NO:748). In other embodiments, the antagonist of IL-1R1 conjugate comprises a
20 V_H dAb that binds human serum albumin and comprises an amino acid sequence selected from the group consisting of DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), and DOM7h-27 (SEQ ID NO:745).

25 The antagonist of IL-1R1 conjugates can comprise any desired antagonist if IL-1R1 moiety (e.g., IL-1ra, functional variant of IL-1ra, dAb) and can be prepared using any suitable methods. For example, the antagonist of IL-1R1 moiety can be bonded to the antigen-binding fragment of an antibody that binds serum albumin directly or indirectly through a suitable linker moiety at one or more positions, such
30 as the amino-terminus, the carboxyl-terminus or through amino acid side chains. In one embodiment, the antagonist of IL-1R1 conjugate comprises a dAb that binds human serum albumin and a polypeptide antagonists of IL-1R1 (e.g., human IL-1ra

or a functional variant of human IL-1ra), and the amino-terminus of the polypeptide antagonists of IL-1R1 (e.g., human IL-1ra or a functional variant of human IL-1ra) is bonded to the carboxyl-terminus of the dAb directly or through a suitable linker moiety. In other embodiments, the conjugate comprises a dAb that binds human
5 serum albumin and two or more different antagonists of IL-1R1 moieties are covalently bonded to the dAb. For example, a first antagonist of IL-1R1 moiety can be covalently bonded (directly or indirectly) to the carboxyl terminus of the dAb and a second antagonist of IL-1R1 moiety can be covalently bonded (directly or indirectly) to the amino-terminus or through a side chain amino group (e.g., ϵ amino
10 group of lysine). Such conjugates can be prepared using well-known methods of selective coupling. (See, e.g., Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).)

A variety of methods for conjugating antagonists of IL-1R1 to an antigen-binding fragment of an antibody that has binding specificity for serum albumin can
15 be used. The particular method selected will depend on the antagonist of IL-1R1 to be conjugated. If desired, linkers that contain terminal functional groups can be used to link the antigen-binding fragment and the antagonist of IL-1R1. Generally, conjugation is accomplished by reacting an antagonist of IL-1R1 that contains a reactive functional group (or is modified to contain a reactive functional group) with
20 a linker or directly with an antigen-binding fragment of an antibody that binds serum albumin. Covalent bonds form by reacting an antagonist of IL-1R1 that contains (or is modified to contain) a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond. If desired, a suitable reactive chemical group can be added to the
25 antigen-binding fragment or to a linker using any suitable method. (See, e.g., Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).) Many suitable reactive chemical group combinations are known in the art, for example an amine group can react with an electrophilic group such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl ester (NHS),
30 and the like. Thiols can react with maleimide, iodoacetyl, acryloyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and

an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)).

5 In some embodiments, the antigen-binding fragment of an antibody that has binding specificity for serum albumin is bonded to an antagonist of IL-1R1 moiety by reaction of two thiols to form a disulfide bond. In other embodiments, the antigen-binding fragment of an antibody that has binding specificity for serum albumin is bonded to an antagonist of IL-1R1 moiety by reaction of an
10 isothiocyanate group and a primary amine to produce an isothioureia bond.

Suitable linker moieties can be linear or branched and include, for example, tetraethylene glycol, C₂-C₁₂ alkylene, -NH-(CH₂)_p-NH- or -(CH₂)_p-NH- (wherein p is one to twelve), -CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-NH-, a polypeptide chain comprising one to about 100 (preferably one to about 12) amino acids and the like.

15

Noncovalent Antagonist of IL-1R1 Conjugates

Some noncovalent bonds (*e.g.*, hydrogen bonds, van der Waals interactions) can produce stable, highly specific intermolecular connections. For example, molecular recognition interactions achieved through multiple noncovalent bonds
20 between complementary binding partners underlie many important biological interactions, such as the binding of enzymes to their substrates, the recognition of antigens by antibodies, the binding of ligands to their receptors, and stabilization of the three dimensional structure of proteins and peptide. Accordingly, such weak noncovalent interactions (*e.g.*, hydrogen bonding, van Der Waals interactions,
25 electrostatic interactions, hydrophobic interactions and the like) can be utilized to bind an antagonist of IL-1R1 to the antigen-binding fragment of an antibody that has binding specificity for serum albumin.

Preferably, the noncovalent bond linking the antigen-binding fragment and antagonist of IL-1R1 be of sufficient strength that the antigen-binding fragment and
30 antagonist of IL-1R1 remain substantially bonded to each under *in vivo* conditions (*e.g.*, when administered to a human). Generally, the noncovalent bond linking the antigen-binding fragment and antagonist of IL-1R1 has a strength of at least about

10^{10} M^{-1} . In preferred embodiments, the strength of the noncovalent bond is at least about 10^{11} M^{-1} , at least about 10^{12} M^{-1} , at least about 10^{13} M^{-1} , at least about 10^{14} M^{-1} or at least about 10^{15} M^{-1} . The interactions between biotin and avidin and between biotin and streptavidin are known to be very efficient and stable under many
5 conditions, and as described herein noncovalent bonds between biotin and avidin or between biotin and streptavidin can be used to prepare a noncovalent antagonist of IL-1R1 conjugate.

The noncovalent bond can be formed directly between the antigen-binding fragment of an antibody that has a specificity for serum albumin and antagonist of
10 IL-1R1, or can be formed between suitable complementary binding partners (*e.g.*, biotin and avidin or streptavidin) wherein one partner is covalently bonded to antagonist of IL-1R1 and the complementary binding partner is covalently bonded to the antigen-binding fragment. When complementary binding partners are employed, one of the binding partners can be covalently bonded to the antagonist of IL-1R1
15 directly or through a suitable linker moiety, and the complementary binding partner can be covalently bonded to the antigen-binding fragment of an antibody that binds serum albumin directly or through a suitable linker moiety.

Complementary binding partners are pairs of molecules that selectively bind to each other. Many complementary binding partners are known in the art, for
20 example, antibody (or an antigen-binding fragment thereof) and its cognate antigen or epitope, enzymes and their substrates, and receptors and their ligands. Preferred complementary binding partners are biotin and avidin, and biotin and streptavidin.

Direct or indirect covalent bonding of a member of a complementary binding pair to an antigen-binding fragment that has binding specificity for serum albumin or
25 an antagonist of IL-1R1 can be accomplished as described above, for example, by reacting a complementary binding partner that contains a reactive functional group (or is modified to contain a reactive functional group) with an antigen-binding fragment of an antibody that binds serum albumin, with or without the use of a linker. The particular method selected will depend on the compounds (*e.g.*,
30 antagonist of IL-1R1, complementary binding partner, antigen-binding fragment of an antibody that binds serum albumin) to be conjugated. If desired, linkers (*e.g.*, homobifunctional linkers, heterobifunctional linkers) that contain terminal reactive

functional groups can be used to link the antigen-binding fragment and/or the antagonist of IL-1R1 to a complementary binding partner. In one embodiment, a heterobifunctional linker that contains two distinct reactive moieties can be used. The heterobifunctional linker can be selected so that one of the reactive moieties
5 will react with the antigen-binding fragment of an antibody that has binding specificity for serum albumin or the antagonist of IL-1R1, and the other reactive moiety will react with the complementary binding partner. Any suitable linker (*e.g.*, heterobifunctional linker) can be used and many such linkers are known in the art and available for commercial sources (*e.g.*, Pierce Biotechnology, Inc., IL).

10

EXAMPLES

Example 1. Immunoglobulin Variable Domain Antagonists of IL-1R1

Methods

15 Selections and screening

For primary selections, 4G-K2 library of V κ dAbs was panned against IL-1R1-Fc fusion protein (Axxora, Nottingham, UK). Domain antibodies from the primary selection were subjected to three further rounds of selection. Round 1 was performed using protein G coated magnetic beads (Dyna, Norway) and 100 nM IL-
20 1R1-Fc; round 2 was performed using anti-human IgG beads (Novagen, Merck Biosciences, Nottingham, UK) and 10 nM IL-1R1-Fc; and round 3 was performed using protein G beads and 1 nM IL-1R1-Fc. (Henderikx *et al.*, Selection of antibodies against biotinylated antigens. Antibody Phage Display : Methods and protocols, Ed. O'Brien and Atkin, Humana Press (2002).) Elution at each stage was
25 with 1 mg/ml trypsin-PBS. For affinity maturation selections, the above method was used, but with the following modifications: two rounds of selection were performed using protein G beads, round 1 using 1 nM IL-1R1-Fc, and round 2 using 100 pM IL-1R1-Fc. Phage vectors from selection outputs (rounds 2 and 3) were isolated by plasmid preps (Qiagen) and dAb inserts were released by restriction
30 digest with *Sal* I and *Not* I. This inserts were ligated into a phage expression vector (*Sal* I/*Not* I cut pDOM5) and used to transform *E. coli* strain HB2151 for soluble expression and screening of dAbs.

Supernatant receptor binding assay (RBA)

Single transformed *E. coli* colonies were picked into 96-well plates containing 2xTY supplemented with 100 µg/ml carbenicillin and 0.1% (w/v) glucose, grown at 37°C to ~OD₆₀₀=0.9 and induced with 1 mM IPTG. Supernatants from overnight inductions at 30°C were screened in a receptor binding assay for the ability to inhibit binding of IL-1β to IL-1RI captured on an ELISA plate. Briefly, MaxiSorp™ immunoassay plates (Nunc, Denmark) were incubated overnight with anti-IL-1RI mouse monoclonal antibody (R&D Systems, Minneapolis, USA). The wells were washed with phosphate buffered saline (PBS) containing 0.1% (v/v) Tween-20 and then blocked with 1% (w/v) BSA in PBS before being incubated with recombinant IL-1RI (500 ng/ml, R&D Systems). The *E. coli* culture supernatants containing dAbs to be screened were placed in the washed wells of the assay plate, the plate was incubated for 30 min, then IL-1β (4 ng/ml, R&D Systems) was added to each well and mixed. IL-1β binding was detected using biotinylated anti-IL-1β antibody (R&D Systems), followed by peroxidase labelled anti-biotin antibody (Stratech, Soham, UK) and then, incubation with 3,3',5,5'-tetramethylbenzidine (TMB) substrate (KPL, Gaithersburg, USA). The reaction was stopped by the addition of HCl and the absorbance was read at 450 nm. Anti-IL-1RI dAb activity caused a decrease in IL-1β binding and therefore a decrease in absorbance compared with the IL-1β only control.

Cell assay

Isolated dAbs were tested for their ability to inhibit IL-1-induced IL-8 release from cultured MRC-5 cells (ATCC catalogue no. CCL-171). Briefly, 5000 trypsinised MRC-5 cells in RPMI media were placed in the well of a tissue-culture microtitre plate and mixed with IL-1α or β (R&D Systems, 200 pg/ml final concentration) and a dilution of the dAb to be tested. The mixture was incubated overnight at 37°C and IL-8 released by the cells into to culture media was quantified in an ELISA (DuoSet®, R&D Systems). Anti-IL-1RI dAb activity caused a decrease in IL-1 binding and a corresponding reduction in IL-8 release.

Human whole blood assay

Whole human blood was incubated with a dilution series of the dAb to be tested, and the mixture was incubated for 30 min at 37°C/5% CO₂. Next, 270 or 900 pM (final concentration) IL-1 α or IL-1 β was added and the mixture, and then the
5 mixtures was incubated at 37°C/5% CO₂ for an additional 20 hours. The blood was then centrifuged (500 x g, 5 min) and the IL-6 released into the supernatant was quantified in an ELISA (DuoSet[®], R&D Systems). Anti-IL-1RI dAb activity caused a decrease in IL-1 binding and a corresponding reduction in IL-6 release.

10 Off-rate screening

These experiments were performed on a BIACORE 3000 surface plasmon resonance instrument, using a CM5 chip (Biacore) coupled with ~600 RU of IL-1RI (R&D Systems). Analytes were passed over the IL-1RI -coated flow-cell, with in-line referencing against a blank flow-cell, at a flow rate of 30 μ l/min in HBS-EP
15 running buffer (Biacore). Ten microlitres of supernatant containing soluble dAb was diluted 1:1 in running buffer, injected (Kinject) at 10 μ l/min flow rate and allowed to dissociate in buffer. Clones with improved off-rates compared to parental clones were identified by eye, or by measurement using BIAevaluation software v4.1.

20

Affinity maturation phage library construction

Two types of libraries were constructed: CDR-re-diversified libraries and error-prone libraries. For the former type of library, PCR reactions were performed, using degenerate oligonucleotides containing NNK or NNS codons, to diversify the
25 required positions in the dAb to be affinity matured. Assembly PCR was then used to generate a full length diversified insert. For the error-prone library, plasmid DNA encoding the dAb to be affinity matured was amplified by PCR, using the GeneMorph[®] II Random Mutagenesis kit (Stratagene). Inserts produced by either method were digested with *Sal* I and *Not* I and used in a ligation reaction with cut
30 phage vector. This ligation was then used to transform *E. coli* strain TB1 by electroporation and the transformed cells were plated on 2xTY agar containing 15 μ g/ml tetracycline, yielding library sizes of $>1 \times 10^8$ clones.

Results

Primary selection and screening

Primary phage selections were performed using the 4G-K2 library and
5 outputs sub-cloned into a soluble expression vector. dAb clones that inhibit binding
of IL-1 to IL-1 RI were identified by supernatant RBA (results not shown), then
expressed, purified by protein L and tested for their ability to inhibit IL-1-induced
IL-8 release in an MRC-5 cell assay. FIG. 1A shows a typical dose-response curve
for anti-IL-1 RI dAb referred to as DOM4-130 in such a cell assay. The ND₅₀ of
10 DOM4-130 in this assay was approximately 500 - 1000 nM. FIG. 1B shows a dose-
response curve for anti-IL-1RI dAbs referred to as DOM4-122 and DOM4-129 in
such a cell assay. The ND₅₀ values of both dAbs was about 1 μ M. DOM4-122 and
DOM4-129 have the same amino acid sequence in CDRs 1 and 2, and have two out
of five amino acid residues identical in CDR3, and therefore were predicted to bind
15 to the same epitope (have the same epitopic specificity) on IL-1R1.

Affinity maturation

DOM4-130

Stage I maturation

20 Using DOM4-130 as a template, a maturation library was constructed with
diversity encoding all 20 amino acids at positions 30, 34, 93 and 94. The resulting
phage library was used in soluble selections for binding to IL-1R1 using IL-1RI-Fc.
Round 2 selection output was cloned into phage expression vector (pDOM5), dAbs
were expressed in *E. coli*, and the expression supernatants were screened for
25 improved off-rates compared to parental dAb. Clones with improved off-rates were
expressed, purified and tested in the MRC-5/IL-8 assay. FIG. 2A depicts a dose-
response curve for improved variant DOM4-130-3, which had an ND₅₀ of about 30
nM.

30 Stage II maturation

Using DOM4-130-3 as template, a maturation library was constructed as
described above, except this time diversity was introduced at amino acid residues

49, 50, 51 and 53 in CDR2. The resulting library was again screened for variants with improved off-rates, which were tested in the MRC-5/IL-8 cell assay. FIG 2B depicts a dose-response curve for improved clone DOM4-130-46 (ND₅₀ about 1 nM), together with an additional variant, DOM4-130-51. DOM4-130-51 was
5 derived from DOM4-130-46, with the mutation S67Y added to improve potency further (ND₅₀ about 300 pM). Further variants of both of these dAbs were produced by introducing the amino acid replacement R107K, to revert the amino acid sequence to the germline sequence at this position, generating DOM4-130-53 and DOM4-130-54, respectively.

10

DOM4-122 and DOM4-129

Stage I maturation

Using DOM4-122 as a template, a maturation library was constructed with diversity encoding all 20 amino acids at positions 28, 30, 31, 92 and 93. In parallel,
15 DOM4-129 was affinity matured by error-prone PCR mutagenesis. The resulting phage libraries were used in soluble selections for binding to IL-1R1 using IL-1RI-Fc. Round 2 and 3 selection outputs were cloned into phage expression vector (pDOM5), dAbs were expressed in *E. coli*, and expression supernatants screened for improved off-rates compared to parent. Clones with improved off-rates were
20 expressed, purified and tested in the MRC-5/IL-8 assay. FIG. 3 depicts a dose-response curve for improved variant DOM4-122-6 and DOM4-129-1, which both had an ND₅₀ value of about 10 nM.

Stage II maturation

25 DOM4-129-1 and DOM4-122-6 gained an amino acid replacement, L46F, in common during maturation. DOM4-129-1 has an additional amino acid replacement, S56R. Both changes were frequently found in clones isolated from maturation selections, therefore the S56R replacement was introduced into DOM4-122-6, yielding DOM4-122-23. DOM4-122-23 had an ND₅₀ of approximately 1
30 nM. An additional amino acid replacement, K45M, gained in both DOM4-122 and DOM4-129 was shown to be non-essential when reverted to the germline amino acid in DOM4-122-23, yielding DOM4-122-24.

Example 2. Antagonists of IL-1R1 are Efficacious in a Subchronic Model of COPD in C57BL/6 mice.

5 In this study, an antagonist of IL-1R1 (and extended half-life fusion protein comprising IL-1ra and a dAb that binds mouse serum albumin), was administered alone or in combination with an antagonists of TNFR1 by the intra-peritoneal injection every 48 hours beginning 24 hours prior to the initial tobacco smoke (TS) exposure. The effects on TS-induced changes in pulmonary inflammatory indices
10 induced by 11 consecutive daily TS exposures were examined 24 hours following the final exposure. The results demonstrate that the antagonist of IL-1R1 was efficacious in the mouse model. ENBREL® (etanercept; Immunex Corporation), which binds TNF and thereby antagonizes TNFR1, was included as a comparator.

Test Compound 1: ENBREL® (etanercept; Immunex Corporation)

15 Test Compound 2: IL-1ra/anti-SA dAb (IL-1ra fused to DOM7m16)

Test Compound 3: 1:1 mixture of PEG DOM1m (anti-TNFR1 dAb comprise an 40 kDa branched polyethylene glycol moiety, TAR2m-21-23) and IL-1ra/anti-SA dAb. For all test substances, the vehicle was sterile saline. Dose volume was 10 ml/kg for test substances 1 - 3 and 20 ml/kg for test substance 4

20 The amino acid sequence of IL-1ra/anti-SA dAb is
RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPI
EPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSNRKQDKRFAFIRS
DSGPTTSFESAACPGWFLCTAMEADQPVS LTNMPDEGVMVTKFYFQEDESS
GGGGSGGGGSGGGGSGGGGSGGGGSTD IQMTQSPSSLSASVGDRV TITCRA
25 QSIIKHLKWKYQQKPGKAPKLLIYGASRLQSGVPSRFRSGSGSGTDFTLTISSL
QPEDFATYYCQQGARWPQTFGQGTKVEIKR (SEQ ID NO:787)

Methods

Female mice (C57BL/6) full barrier bred and certified free of specific micro
30 organisms on receipt (16-20g) (Charles River) were housed in groups of up to 5 in

individually ventilated, solid bottomed cages (IVC) with aspen chip bedding. Environments (airflow, temperature and humidity) within the cages were controlled by the IVC system (Techniplast).

There were 5 treatment groups, groups 1-4 contained 10 animals and group 5 contained 5 animals. The treatment groups are summarized in Table 1. All treatments were administered intraperitoneally, and the dose volume for groups 1-4 was 10 ml/kg and was 20 ml/kg for group 5. Treatments were administered every 48 hours, and the initial dose was administered 24 hours prior to the initial TS or air exposure. Subsequent treatment doses were administered 1 hour prior to each TS or air exposure.

Table 1

Group No.	TS / Air Exposure	Compound No.	Dose mg/kg
1	Sham	Vehicle	0
2	TS	Vehicle	0
3	TS	1	10
4	TS	2	10
5	TS	3	20

TS exposure

Mice (maximum 5 per exposure chamber) were exposed to TS generated from cigarettes (Type 1R1, supplied by University of Kentucky). Initial exposure was to 4 cigarettes on day 1, increasing to a maximum of 6 cigarettes per day by day 6/7. Exposure thereafter to day 11 was 6 cigarettes/day. The rate of increase was regulated with regard to the daily observed tolerance of the mice. The control group of mice was exposed to air for an equivalent length of time on each exposure day (air exposure controls).

Health monitoring:

Animals were weighed prior to the start of the study, on day 6 of the exposure protocol, and at the time of termination. All animals were monitored during and after each test substance administration and TS exposure.

Terminal procedures:

Animals were sacrificed by anaesthetic overdose (pentobarbitone Na, 100mg/kg i.p.) as follows: All groups were sacrificed 24 hours after the 11th and final TS exposure. Mice from all treatment groups were treated as follows: Blood
5 samples were taken from the sub-clavian artery, placed in a microcentrifuge tube and allowed to clot overnight at 4°C. The clot was removed and the remaining fluid was centrifuged at 2900 rpm in a microcentrifuge for 6 minutes. The resulting supernatant serum was decanted and stored at -40°C for possible PK analysis. A bronchoalveolar lavage (BAL) was performed using 0.4 ml of phosphate buffered
10 saline (PBS). Cells recovered from the BAL were quantified by total and differential cell counts. Lungs were removed, snap frozen in liquid nitrogen and stored at -80°C for possible PK analysis

Data Analysis

15 A test for normality was carried out on the data. If the test was positive, then a preliminary analysis was carried out using a one way analysis of variance test (one way ANOVA) followed by a Bonferroni's multiple comparison post test to compare control and treatment groups. If the data was not normally distributed, then a Kruskal-Wallis test followed by Dunn's multiple comparisons test was employed.
20 Data were considered significant when $p < 0.05$.

Results

The IL-1ra/SA dAb treatment groups, show significantly reduced cell infiltrates in the lung compared to the TS exposed and vehicle treated control group
25 (FIG. 5). The level of cells in the lung was reduced by 58% for total cells ($p < 0.01$), 56% for macrophages ($p < 0.001$), 59% for polymorphic nuclear cells ($p < 0.01$), 70% for eosinophils ($p < 0.01$), and 65% for lymphocytes ($p < 0.01$). A 29% reduction in epithelial cells was observed but this change was not significant.

The combination treatment group with IL1ra/SA dAb and PEGylated anti-
30 TNFR1 dAb, show significantly reduced cell infiltrates in the lung. 88% inhibition for total cells ($p < 0.001$), 82% for macrophages, 94% for epithelial cells, 93% for polymorphic nuclear cells, 93% for eosinophils and 86% for lymphocytes.

No significant reductions in any of the cell populations were observed in the ENBREL® (etanercept; Immunex Corporation) treated group. ENBREL® (etanercept; Immunex Corporation) even led to an increased number of total cells, although the increase was not statistically significant (FIG. 5).

5

Example 3. Local Administration of an Immunoglobulin Variable Domain to Pulmonary Tissue.

In this study, an domain antibody (V_H) that binds hen egg lysozyme was administered locally to pulmonary tissue by intranasal administration, and pharmacokinetics were determined. The results demonstrate that domain antibodies can be delivered locally to pulmonary tissue model.

Methods

Female mice (C57BL/6) full barrier bred and certified free of specific micro organisms on receipt (16-20g) (Charles River) were housed in groups of up to 5 in individually ventilated, solid bottomed cages (IVC) with aspen chip bedding. Environments (airflow, temperature and humidity) within the cages were controlled by the IVC system (Techniplast).

The domain antibody HEL4 is a V_H that binds Hen egg lysozyme. (See, Jespers et al. J. Mol. Biol., 337:893-903 (2004). HEL-4 monomer (12 mg/ml) which contained an HA tag for detection was diluted in 20 mM sodium citrate pH 6.0, 100 mM NaCl. Mice were lightly anaesthetised (Isofluorane/ O_2) and 50 microliters of dAb solution or vehicle control was dropped gently onto the nares. The animals were held in an upright position for a few seconds while spontaneously breathing in the solution before being allowed to recover and returned to their cages.

Treatment Groups

There were 17 groups, the groups administered HEL-4 each contained 3 mice, while the vehicle control groups each contained two mice. The dose volume was 50 μ l (25 μ l / nare), and all mice were treated on the same day. Mice were sacrificed 1, 2, 5, 8 or 24 hours after treatment was administered (8 hours and 24

hours after treatment for vehicle groups). The study protocol is summarized in Table 2.

Table 2

Group No.	Treatment	Dose	Concentration mg/ml	Sacrifice time after administration
1	HEL-4	30 mg/kg	12 mg/ml	1
2	HEL-4	30 mg/kg	12 mg/ml	2
3	HEL-4	30 mg/kg	12 mg/ml	5
4	HEL-4	30 mg/kg	12 mg/ml	8
5	HEL-4	30 mg/kg	12 mg/ml	24
6	HEL-4	3 mg/kg	1.2 mg/ml	1
7	HEL-4	3 mg/kg	1.2 mg/ml	2
8	HEL-4	3 mg/kg	1.2 mg/ml	5
9	HEL-4	3 mg/kg	1.2 mg/ml	8
10	HEL-4	3 mg/kg	1.2 mg/ml	24
11	HEL-4	1 mg/kg	0.4 mg/ml	1
12	HEL-4	1 mg/kg	0.4 mg/ml	2
13	HEL-4	1 mg/kg	0.4 mg/ml	5
14	HEL-4	1 mg/kg	0.4 mg/ml	8
15	HEL-4	1 mg/kg	0.4 mg/ml	24
16	Vehicle	50 µl/mouse	0	8
17	Vehicle	50 µl/mouse	0	24

5 Health monitoring

Animals were weighed prior to the start of the study. All animals were monitored during and after each administration. Animals in the 24 hour groups were monitored at regular intervals overnight.

10 Terminal procedures

Animals were sacrificed by anaesthetic overdose (pentobarbitone Na, 100mg/kg i.p.). Blood was taken from the subclavian artery, placed in a

microcentrifuge tube and allowed to clot overnight at 4°C. The clot was gently removed and the remaining fluid was centrifuged at 2900 rpm in a microcentrifuge for 6 minutes. The resulting supernatant was decanted, placed in a fresh tube, frozen and stored at -40°C prior to analysis. Bronchoalveolar lavage (BAL) was conducted using 0.4 ml of phosphate buffered saline (PBS) which was instilled and withdrawn 3 times. The BAL was centrifuged at 2700 rpm in a microcentrifuge for 6 minutes and the supernatant removed and stored at -40°C prior to analysis. The cell pellet was re-suspended in a suitable volume of PBS and total cell count determined using a haemocytometer. Cytospin slides were prepared for differential cell determinations. The lungs were excised, snap frozen and stored at -80°C prior to analysis. Using a mortar and pestle lungs were pulverized under liquid nitrogen and dissolved in T-PER® Tissue Protein Extraction Reagent (Pierce) and homogenized using 40 strokes with a dounce homogenizer.

ELISA to detect HA tagged HEL-4

A 96 well Maxisorp (Nunc) assay plate was coated overnight at 4°C with 100µl per well of goat polyclonal anti HA tag antibody (Abcam) at 2µg/ml in carbonate buffer. Wells were washed 3 times with 0.05% tween/PBS and 3 times with PBS. 200µl per well of 2% BSA in PBS was added to block the plate. After blocking, wells are washed and then 100µl of HA tagged dAb standard or sample was added. Wells were washed and then 100µl Protein A – HRP (1:5000 dilution; Amersham) was added to each well. Plates were developed by adding 100µl of SureBlue 1-Component TMB MicroWell Peroxidase (KPL, Gaithersburg, USA) solution to each well, and the plate was left at room temperature until a suitable signal has developed. The reaction was stopped by the addition of HCl and absorbance was read at 450 nm.

Results

The total BAL cell counts showed that administering HEL-4 domain antibody at doses of 1, 3 or 30 mg/kg did not cause significant inflammation in the lungs. Some of the animals had increased cellular infiltrates but these were not significantly different from animals treated with vehicle alone. The HEL-4 levels in

the BAL show that the dAbs are delivered efficiently into the deep lung (FIG. 6). A dose related effect was observed. At 2 hours after administration, a maximum level of 700ug/ml was detected in the lung with the 30 mg/kg dosing. Thus, about 48% (280 μ g of 600 μ g total delivered) of the administered material was recovered from the lung, which means that more than 48% material that was administered was delivered to the lung but not all dAb delivered to the lung can be recovered, or is present in the surrounding tissues. The levels in the BAL are high for a prolonged period of time and there appears to be a slow release into the surrounding tissues.

HEL-4 serum levels were detected in the 3 mg/kg and the 30 mg/kg dose groups (FIG. 7). The serum levels showed a similar pattern as the BAL levels. There appears to be a maximum level 2 hours after administration, followed by a slow decline. At 2 hours after administration, maximum levels of 3.5 μ g/ml were detected in the serum with the 30 mg/kg dosing. This means that about 1% (5 μ g of 600 μ g administered) of the administered material was detected in the serum.

15

Example 4. Local Administration of an Antagonist of IL-1R1 to Pulmonary Tissue.

In this study the antagonist of IL-1R1, KINARET[®] (anakinra; Amgen) a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra) that differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus, was administered by intra-nasal administration, and pharmacokinetics were evaluated.

Methods

KINARET[®] (anakinra; Amgen) was diluted in 20 mM sodium citrate pH6.0, 100 mM NaCl. All animals were treated on the same day within 1 to 2 hours of warming the solution.

Female mice (C57BL/6) full barrier bred and certified free of specific micro organisms on receipt (16-20g) (Charles River) were housed in groups of up to 5 in individually ventilated, solid bottomed cages (IVC) with aspen chip bedding. Environments (airflow, temperature and humidity) within the cages were controlled by the IVC system (Techniplast).

There were 5 treatment groups, and each group contained 3 animals. The treatment groups are summarized in Table 3. All treatments were administered intranasally, and the dose volume was 50 microliters (25 microliteres per nare). Mice were sacrificed 1, 2, 5, 8, or 24 hours after administration.

5

Table 3

10

Group No.	Dose	Concentration mg/ml	Sacrifice time after administration
1	1 mg/kg	0.4mg/ml	1
2	1 mg/kg	0.4mg/ml	2
3	1 mg/kg	0.4mg/ml	5
4	1 mg/kg	0.4mg/ml	8
5	1 mg/kg	0.4mg/ml	24

15

ELISA to detect IL1ra.

A 96 well Maxisorp (Nunc) assay plate was coated overnight at 4°C with 50µl per well with mouse anti-human IL1R1 antibody (R&D systems) at 4µg/ml in carbonate coating buffer pH 9.4. Wells were washed 3 times with 0.05% tween/PBS and 3 times with PBS. 200µl per well of 1% BSA in PBS was added to block the plate for 1 hour. Wells were washed and then 100µl of IL1 R1 at 500ng/ml (R&D systems) was added in 0.1% BSA/0.05% tween/PBS for 1 hour. Wells were washed and then 100µl of IL1ra standard or sample was added in 0.1% BSA/0.05% tween/PBS. IL1ra standard and samples were incubated with the receptor for 30 minutes. IL-1 β was then added (R&D Systems) at a final concentration of 4ng/mL and plates were incubated for another hour. Wells were washed and bound IL-1 β was detected with biotinylated anti IL-1 β antibody (R&D systems) at 0.5µg/ml in 0.1% BSA/0.05% tween/PBS for 1 hour. Wells were washed and then 100µl of anti-biotin-HRP antibody was added (Stratech)(1/5000 in 0.1% BSA/0.05% tween/PBS) for 1 hour. Plates were developed with 100µl of SureBlue 1-Component TMB MicroWell Peroxidase (KPL, Gaithersburg, USA) solution was added to each well, and the plate was left at room temperature until a suitable signal

30

has developed (~15 minutes). The reaction was stopped by the addition of HCl and the absorbance was read at 450 nm.

Results

5 The level in the BAL (FIG. 8) was maximum at 1 hour after administration and was ~ 11 µg/ml (~2.75 µg in 0.25 ml of BAL fluid). This means that at least 14% (2.75 µg of 20 µg total administered) of the administered material is delivered in the lung. More material will be present in the surrounding tissues but this cannot be recovered. The levels in the BAL are high for a prolonged period of time and show a
10 gradual decline over 24hrs. (> 10-fold decline after 24 hrs).

 The levels in the lung (FIG. 8) is maximum at 1hr and was ~ 3.3 µg/ml. This means that at least 16% (3.3 µg of 20 µg total administered) of the administered material is present in the lung. The levels in the lung are high for a prolonged period of time and show a gradual decline over 24hrs. (> 10-fold decline after 24 hrs).

15 The level in the serum (FIG. 8) at 1 hr was ~260 ng/ml. At 5 hrs the levels in the serum was maximum (350 ng/ml). This means that the percentage of the total delivered dose present in the serum at 5 hrs is ~2.6% (Total dose administered was 20 µg; 1.5 ml of blood volume). The levels in the serum show a slow decline and after 24hrs there is only a 5-fold decline in the levels.

20

Example 5. Local Administration of Antagonists of IL-1R1 to Pulmonary Tissue in a Subchronic Model of COPD in C57BL/6 mice.

 In view of the demonstrated ability to locally administer an antagonist to the
25 lung by intranasal administration, a pilot study to assess this delivery route in a disease model was conducted. In this study, Il1ra was administered by the intranasal route 1 hour prior to each air or TS exposure. The effects on tobacco smoke (TS) induced changes in pulmonary inflammatory indices induced by 11 consecutive daily TS exposures was examined 24 h following the final exposure. The anti-TNF
30 compound ENBREL® (etanercept; Immunex Corporation) was used as a positive control.

Test Substance 1: ENBREL® (etanercept; Immunex Corporation)

Test Substance 2: KINARET® (anakinra; Amgen)

The vehicle was sterile sodium citrate pH6.0, 100mM NaCl.

5 Methods

Female mice (C57BL/6) full barrier bred and certified free of specific micro organisms on receipt (16-20g) (Charles River) were housed in groups of up to 5 in individually ventilated, solid bottomed cages (IVC) with aspen chip bedding. Environments (airflow, temperature and humidity) within the cages were controlled
10 by the IVC system (Techniplast).

There were 4 treatment groups, and each group contained 10 animals. The treatment groups are summarized in Table 4. All treatments were administered intranasally, and the dose volume was 50 microliters (25 microliteres per nare). Mice were sacrificed 1, 2, 5, 8, or 24 hours after administration. Treatments were
15 administered every 1 hour prior to each TS or air exposure.

Table 4

Group No.	TS / Air Exposure	Compound No.	Dose mg/kg
1	Air	Vehicle	0
2	TS	Vehicle	0
3	TS	1	1.0
4	TS	2	1.0

20 TS exposure

Mice (maximum 5 per exposure chamber) were exposed to TS generated from cigarettes (Type 1R1, supplied by University of Kentucky). Initial exposure was to 4 cigarettes on day 1, increasing to a maximum of 6 cigarettes per day by day 6/7. Exposure thereafter to Day 11 was to 6 cigarettes per day. The rate of increase
25 was regulated with regard to the daily observed tolerance of the mice. The control

group of mice was exposed to air for an equivalent length of time on each exposure day (Air exposure).

Health monitoring:

- 5 Animals were weighed prior to the start of the study, on day 6 of the exposure protocol, and at the time of termination. All animals were monitored during and after each test substance administration and TS exposure.

Terminal procedures:

- 10 Animals were sacrificed by anaesthetic overdose (pentobarbitone Na, 100mg/kg i.p.) as follows: All groups were sacrificed 24 hours after the 11th and final TS exposure. Mice from all treatment groups were treated as follows: Blood samples were taken from the sub-clavian artery, placed in a microcentrifuge tube and allowed to clot overnight at 4°C. The clot was removed and the remaining fluid
15 was centrifuged at 2900 rpm in a microcentrifuge for 6 minutes. The resulting supernatant serum was decanted and stored at -40°C for possible PK analysis. A bronchoalveolar lavage (BAL) was performed using 0.4 ml of phosphate buffered saline (PBS). Cells recovered from the BAL were quantified by total and differential cell counts. Lungs were removed, snap frozen in liquid nitrogen and
20 stored at -80°C for possible PK analysis

Data Analysis

- A test for normality was carried out on the data. If the test was positive, then a preliminary analysis was carried out using a one way analysis of variance test (one
25 way ANOVA) followed by a Bonferroni's multiple comparison post test to compare control and treatment groups. If the data was not normally distributed, then a Kruskal-Wallis test followed by Dunn's multiple comparisons test was employed. Data were considered significant when $p < 0.05$.

30 Results

 This pilot study was conducted to evaluate local delivery of antagonists of IL-1R1 to pulmonary tissue in a model of respiratory disease. The results showed

that the level of total cells in group treated with KINARET[®] (anakinra; Amgen) were 29% lower (and 11% lower in the group treated with ENBREL[®] (etanercept; Immunex Corporation)) than in the control group that was exposed to TS by administered vehicle. Although the changes observed in this pilot study did not
5 achieve statistical significance, the results indicate that polypeptide antagonists can be locally administered to pulmonary tissue.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled
10 in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. Use of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1) for
5 the manufacture of a medicament for treating a respiratory disease, wherein said
antagonist of IL-1R1 comprises a polypeptide domain that has binding specificity
for Interleukin-1 Receptor Type 1 (IL-1R1) and inhibits binding of Interleukin-1
(IL-1) to IL-1R1, and wherein said polypeptide domain that has binding specificity
for IL-1R1 is provided by an antibody or antigen-binding fragment thereof,
10 Interleukin-1 receptor antagonist (IL-1ra) or a functional variant of IL-1ra.
2. The use of claim 1, wherein said polypeptide domain that has binding
specificity for IL-1R1 inhibits binding of IL-1 to IL-1R1 with an IC50 that is ≤ 1
 μM .
15
3. The use of claim 1, wherein said polypeptide domain that has binding
specificity for IL-1R1 inhibits IL-1-induced release of Interleukin-8 by MRC-5 cells
(ATCC Accession No. CCL-171) in an *in vitro* assay with a ND50 that is $\leq 1 \mu\text{M}$.
- 20 4. The use of claim 4, wherein said polypeptide domain that has binding
specificity for IL-1R1 inhibits IL-1-induced release of Interleukin-8 by MRC-5 cells
(ATCC Accession No. CCL-171) in an *in vitro* assay with a ND50 that is $\leq 1 \text{ nM}$.
5. The use of claim 1, wherein said polypeptide domain that has binding
25 specificity for IL-1R1 inhibits IL-1-induced release of Interleukin-6 in a whole
blood assay with a ND50 that is $\leq 1 \mu\text{M}$.
6. The use of any one of claims 1-5, wherein said polypeptide domain
that has binding specificity for IL-1R1 is an antigen-binding fragment of an
30 antibody, and said antigen-binding fragment is an immunoglobulin single variable
domain.

7. The use of claim 6, wherein one or more of the framework regions (FR) in said immunoglobulin single variable domain comprise (a) the amino acid sequence of a human framework region, (b) at least 8 contiguous amino acids of the amino acid sequence of a human framework region, or (c) an amino acid sequence
5 encoded by a human germline antibody gene segment, wherein said framework regions are as defined by Kabat.
8. The use of claim 6, wherein the amino acid sequences of one or more framework regions in said immunoglobulin single variable domain are the same as
10 the amino acid sequence of a corresponding framework region encoded by a human germline antibody gene segment, or the amino acid sequences of one or more of said framework regions collectively comprise up to 5 amino acid differences relative to the corresponding framework regions encoded by a human germline antibody gene segment.
- 15 9. The use of claim 6, wherein the amino acid sequences of FR1, FR2, FR3 and FR4 in said immunoglobulin single variable domain are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment, or the amino acid sequences of FR1, FR2, FR3 and
20 FR4 collectively contain up to 10 amino acid differences relative to the corresponding framework regions encoded by a human germline antibody gene segment.
10. The use of claim 6, wherein the immunoglobulin single variable
25 domain comprises FR1, FR2 and FR3 regions, and the amino acid sequence of said FR1, FR2 and FR3 are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment.
11. The use of any one of claims 7-10, wherein said human germline
30 antibody gene segment comprises is DPK9 and JK1.

12. The use of any one of claims 6-11, wherein said immunoglobulin single variable domain competes for binding to IL-1R1 with an immunoglobulin single variable domain selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109

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13. The use of claim 12, wherein said immunoglobulin single variable domain comprises an amino acid sequence that has at least about 90% amino acid sequence identity with an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID

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14. The use of any one of claims 1-14, wherein said polypeptide domain that has binding specificity for IL-1R1 binds human IL-1R1 with an affinity (KD) of about 300 nM to about 5 pM, as determined by surface plasmon resonance.

15. The use of any one of claims 1-14, wherein said antagonist of IL-1R1 further comprises a half-life extending moiety.

16. The use of claim 15, wherein said half-life extending moiety is a polyalkylene glycol moiety, serum albumin or a fragment thereof, transferrin receptor or a transferrin-binding portion thereof, or an antibody or antibody fragment comprising a binding site for a polypeptide that enhances half-life *in vivo*.

17. The use of claim 16, wherein said half-life extending moiety is a polyethylene glycol moiety.

18. The use of claim 16, wherein said half-life extending moiety is an antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc receptor.

19. The use of claim 18, wherein said antibody or antibody fragment is an antibody fragment, and said antibody fragment is an immunoglobulin single variable domain.

20. The use of claim 19, wherein said immunoglobulin single variable domain competes with an immunoglobulin single variable domain selected from the

group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732),
5 DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749),
10 DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784), for binding to human serum albumin.

25

21. The use of claim 20, wherein said immunoglobulin single variable domain binds human serum albumin comprises an amino acid sequence selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6
30

(SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746),
5 DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762),
10 DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784).

20

22. The use of any one of claims 1-21, wherein said antagonist of IL-1R1 further comprises a polypeptide binding domain that has binding specificity for Tumor Necrosis Factor Receptor 1 (TNFR1, p55) and inhibits binding of Tumor Necrosis Factor Alpha (TNF α) to TNFR1.

25

23. The use of any one of claims 1-22, wherein said antagonist of IL-1R1 binds human IL-1R1 with an affinity (KD) of about 300 nM to about 5 pM, as determined by surface plasmon resonance.

30

24. The use of any one of claims 1-23, wherein said respiratory disease is selected from the group consisting of lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary

infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, sarcoidosis, and Wegener's granulomatosis.

15

25. The use of any one of claims 1-24, wherein the medicament is for administration together with an antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1, p55), or further comprises an antagonist of TNFR1.

20

26. The use of any one of claims 1-24, wherein said medicament is for treating a respiratory disease by systemic administration of the medicament.

25

27. The use of claim 26, wherein said medicament is for treating a respiratory disease by systemic administration of the medicament, wherein systemic administration is intraperitoneal or subcutaneous administration.

30

28. The use of any one of claims 1-24, wherein said medicament is for treating a respiratory disease by local administration of said medicament to pulmonary tissue.

29. The use of claim 28, wherein said medicament is for treating a respiratory disease by local administration of said medicament to pulmonary tissue by inhalation or intranasal administration.

5 30. The use of any one of claims 1-29, wherein the level of inflammatory cells in the lung is assessed by total cell counts in bronchoalveolar lavage, sputum or bronchial biopsy is reduced relative to pretreatment levels.

31. The use of claim 30, wherein the level of inflammatory cells in the
10 lung is assessed by macrophage, polymorphonuclear, lymphocyte and/or eosinophil cell counts in bronchoalveolar lavage, sputum or bronchial biopsy.

32. Use of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1) for the manufacture of a medicament for treating a respiratory disease, wherein said
15 antagonist of IL-1R1 is a fusion protein or a conjugate comprising an antagonist of IL-1R1 moiety and a half-life extending moiety, wherein said antagonist of IL-1R1 moiety binds human IL-1R1 and inhibits binding of Interleukin-1 to human IL-1R1, and said half-life extending moiety is a polypeptide binding moiety that contains a binding site with binding specificity for a polypeptide that enhances serum half-life
20 *in vivo*.

33. The use of claim 32, wherein said antagonist of IL-1R1 moiety is human Interleukin 1 receptor antagonist (IL-1ra) or a functional variant of human IL-1ra.

25

34. The use of claim 33, wherein said antagonist of IL-1R1 moiety is an immunoglobulin single variable domain that competes for binding to IL-1R1 with an immunoglobulin single variable domain selected from the group consisting of
30 DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID

NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113 (SEQ ID NO:86), DOM4-114 (SEQ ID NO:87), DOM4-115 (SEQ ID NO:88), DOM4-116 (SEQ ID NO:89), DOM4-117 (SEQ ID NO:90), DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99),

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35. The use of claim 33, wherein said antagonist of IL-1R1 moiety is an immunoglobulin single variable domain that comprises an amino acid sequence that has at least about 90% amino acid sequence identity with an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-

45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46),
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36. The use of any one of claims 32-35, said half-life extending moiety is serum albumin or a fragment thereof, transferrin receptor or a transferrin-binding portion thereof, or an antibody or antibody fragment comprising a binding site for a polypeptide that enhances half-life *in vivo*.

37. The use of claim 36, wherein said half-life extending moiety is an antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc receptor.

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38. The use of claim 37, wherein said antibody or antibody fragment is an antibody fragment, and said antibody fragment is an immunoglobulin single variable domain.

15 39. The use of claim 38, wherein said immunoglobulin single variable domain competes with an immunoglobulin single variable domain selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765),

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DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784) for binding to human serum albumin.

40. The use of claim 38, wherein said immunoglobulin single variable domain binds human serum albumin comprises an amino acid sequence selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K

(SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784).

5 41. The use of any one of claims 32-40, wherein said respiratory disease
is selected from the group consisting of lung inflammation, chronic obstructive
pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary
infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis,
cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary
10 thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders
of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory
distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease,
lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis,
bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic
15 pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous
mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia,
pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax,
pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary
histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary
20 tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease,
sarcoidosis, and Wegener's granulomatosis.

42. Use of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1) for
the manufacture of a medicament for treating a respiratory disease, wherein said
25 antagonist of IL-1R1 comprises an immunoglobulin single variable domain that has
binding specificity for human IL-1R1 and inhibits binding of Interleukin-1 (IL-1) to
human IL-1R1, and a polyethylene glycol moiety.

43. The use of claim 42, wherein said immunoglobulin single variable
30 domain competes for binding to human IL-1R1 with an immunoglobulin single
variable domain selected from the group consisting of DOM4-122-23 (SEQ ID
NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-
130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID

NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11
5 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31
10 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49
15 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87
20 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101
25 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113 (SEQ ID NO:86), DOM4-114 (SEQ ID NO:87), DOM4-115 (SEQ ID NO:88), DOM4-116 (SEQ ID NO:89), DOM4-117
30 (SEQ ID NO:90), DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID

NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102), DOM4-122-8 (SEQ ID NO:103), DOM4-122-9 (SEQ ID NO:104), DOM4-122-10 (SEQ ID NO:105), DOM4-122-11 (SEQ ID NO:106), DOM4-122-12 (SEQ ID NO:107), DOM4-122-13 (SEQ ID NO:108), DOM4-122-14 (SEQ ID NO:109), DOM4-122-15 (SEQ ID NO:110), DOM4-122-16 (SEQ ID NO:111), DOM4-122-17 (SEQ ID NO:112), DOM4-122-18 (SEQ ID NO:113), DOM4-122-19 (SEQ ID NO:114), DOM4-122-20 (SEQ ID NO:115), DOM4-122-21 (SEQ ID NO:116), DOM4-122-22 (SEQ ID NO:117), DOM4-122-25 (SEQ ID NO:118), DOM4-122-26 (SEQ ID NO:119), DOM4-122-27 (SEQ ID NO:120), DOM4-122-28 (SEQ ID NO:121), DOM4-122-29 (SEQ ID NO:122), DOM4-122-30 (SEQ ID NO:123), DOM4-122-31 (SEQ ID NO:124), DOM4-122-32 (SEQ ID NO:125), DOM4-122-33 (SEQ ID NO:126), DOM4-122-34 (SEQ ID NO:127), DOM4-122-35 (SEQ ID NO:128), DOM4-122-36 (SEQ ID NO:129), DOM4-122-37 (SEQ ID NO:130), DOM4-122-38 (SEQ ID NO:131), DOM4-122-39 (SEQ ID NO:132), DOM4-122-40 (SEQ ID NO:133), DOM4-122-41 (SEQ ID NO:134), DOM4-122-42 (SEQ ID NO:135), DOM4-122-43 (SEQ ID NO:136), DOM4-122-44 (SEQ ID NO:137), DOM4-122-45 (SEQ ID NO:138), DOM4-122-46 (SEQ ID NO:139), DOM4-122-47 (SEQ ID NO:140), DOM4-122-48 (SEQ ID NO:141), DOM4-122-49 (SEQ ID NO:142), DOM4-122-50 (SEQ ID NO:143), DOM4-122-51 (SEQ ID NO:144), DOM4-122-52 (SEQ ID NO:145), DOM4-122-54 (SEQ ID NO:146), DOM4-122-55 (SEQ ID NO:147), DOM4-122-56 (SEQ ID NO:148), DOM4-122-57 (SEQ ID NO:149), DOM4-122-58 (SEQ ID NO:150), DOM4-122-59 (SEQ ID NO:151), DOM4-122-60 (SEQ ID NO:152), DOM4-122-61 (SEQ ID NO:153), DOM4-122-62 (SEQ ID NO:154), DOM4-122-63 (SEQ ID NO:155), DOM4-122-64 (SEQ ID NO:156), DOM4-122-65 (SEQ ID NO:157), DOM4-122-66 (SEQ ID NO:158), DOM4-122-67 (SEQ ID NO:159), DOM4-122-68 (SEQ ID NO:160), DOM4-122-69 (SEQ ID NO:161), DOM4-122-70 (SEQ ID NO:162), DOM4-122-71 (SEQ ID NO:163), DOM4-122-72 (SEQ ID NO:164), DOM4-122-73 (SEQ ID NO:165), DOM4-123 (SEQ ID NO:166), DOM4-124 (SEQ ID NO:167) DOM4-125 (SEQ ID NO:168), DOM4-126 (SEQ ID NO:169), DOM4-127 (SEQ ID NO:170), DOM4-

128 (SEQ ID NO:171), DOM4-129 (SEQ ID NO:172), DOM4-129-1 (SEQ ID NO:173,) DOM4-129-2 (SEQ ID NO:174), DOM4-129-3 (SEQ ID NO:175), DOM4-129-4 (SEQ ID NO:176), DOM4-129-5 (SEQ ID NO:177), DOM4-129-6 (SEQ ID NO:178), DOM4-129-7 (SEQ ID NO:179), DOM4-129-8 (SEQ ID NO:180), DOM4-129-9 (SEQ ID NO:181), DOM4-129-10 (SEQ ID NO:182), DOM4-129-11 (SEQ ID NO:183), DOM4-129-12 (SEQ ID NO:184), DOM4-129-13 (SEQ ID NO:185), DOM4-129-14 (SEQ ID NO:186), DOM4-129-15 (SEQ ID NO:187), DOM4-129-16 (SEQ ID NO:188), DOM4-129-17 (SEQ ID NO:189), DOM4-129-18 (SEQ ID NO:190), DOM4-129-19 (SEQ ID NO:191), DOM4-129-20 (SEQ ID NO:192), DOM4-129-21 (SEQ ID NO:193), DOM4-129-22 (SEQ ID NO:194), DOM4-129-23 (SEQ ID NO:195), DOM4-129-24 (SEQ ID NO:196), DOM4-129-25 (SEQ ID NO:197), DOM4-129-26 (SEQ ID NO:198), DOM4-129-27 (SEQ ID NO:199), DOM4-129-28 (SEQ ID NO:200), DOM4-129-29 (SEQ ID NO:201), DOM4-129-31 (SEQ ID NO:202), DOM4-129-32 (SEQ ID NO:203), DOM4-129-33 (SEQ ID NO:204), DOM4-129-34 (SEQ ID NO:205), DOM4-129-35 (SEQ ID NO:206), DOM4-129-37 (SEQ ID NO:207), DOM4-129-38 (SEQ ID NO:208), DOM4-129-39 (SEQ ID NO:209), DOM4-129-40 (SEQ ID NO:210), DOM4-129-41 (SEQ ID NO:211), DOM4-129-42 (SEQ ID NO:212), DOM4-129-43 (SEQ ID NO:213), DOM4-129-44 (SEQ ID NO:214), DOM4-130 (SEQ ID NO:215), DOM4-130-1 (SEQ ID NO:216), DOM4-130-2 (SEQ ID NO:217), DOM4-130-3 (SEQ ID NO:218), DOM4-130-4 (SEQ ID NO:219), DOM4-130-5 (SEQ ID NO:220), DOM4-130-6 (SEQ ID NO:221), DOM4-130-7 (SEQ ID NO:222), DOM4-130-8 (SEQ ID NO:223), DOM4-130-9 (SEQ ID NO:224), DOM4-130-10 (SEQ ID NO:225), DOM4-130-11 (SEQ ID NO:226), DOM4-130-12 (SEQ ID NO:227), DOM4-130-13 (SEQ ID NO:228), DOM4-130-14 (SEQ ID NO:229), DOM4-130-15 (SEQ ID NO:230), DOM4-130-16 (SEQ ID NO:231), DOM4-130-17 (SEQ ID NO:232), DOM4-130-18 (SEQ ID NO:233), DOM4-130-19 (SEQ ID NO:234), DOM4-130-20 (SEQ ID NO:235), DOM4-130-21 (SEQ ID NO:236), DOM4-130-22 (SEQ ID NO:237), DOM4-130-23 (SEQ ID NO:238), DOM4-130-24 (SEQ ID NO:239), DOM4-130-25 (SEQ ID NO:240), DOM4-130-26 (SEQ ID NO:241), DOM4-130-27 (SEQ ID NO:242), DOM4-130-28 (SEQ ID NO:243), DOM4-130-31 (SEQ ID NO:244), DOM4-130-32 (SEQ ID NO:245),

DOM4-130-33 (SEQ ID NO:246), DOM4-130-34 (SEQ ID NO:247), DOM4-130-35 (SEQ ID NO:248), DOM4-130-36 (SEQ ID NO:249), DOM4-130-37 (SEQ ID NO:250), DOM4-130-38 (SEQ ID NO:251), DOM4-130-39 (SEQ ID NO:252), DOM4-130-40 (SEQ ID NO:253), DOM4-130-41 (SEQ ID NO:254), DOM4-130-42 (SEQ ID NO:255), DOM4-130-43 (SEQ ID NO:256), DOM4-130-44 (SEQ ID NO:257), DOM4-130-45 (SEQ ID NO:258), DOM4-130-46 (SEQ ID NO:259), DOM4-130-47 (SEQ ID NO:260), DOM4-130-48 (SEQ ID NO:261), DOM4-130-49 (SEQ ID NO:262), DOM4-130-50 (SEQ ID NO:263), DOM4-130-51 (SEQ ID NO:264), DOM4-130-52 (SEQ ID NO:265), DOM4-130-53 (SEQ ID NO:266), DOM4-130-54 (SEQ ID NO:267), DOM4-130-55 (SEQ ID NO:268), DOM4-130-56 (SEQ ID NO:269), DOM4-130-57 (SEQ ID NO:270), DOM4-130-58 (SEQ ID NO:271), DOM4-130-59 (SEQ ID NO:272), DOM4-130-60 (SEQ ID NO:273), DOM4-130-61 (SEQ ID NO:274), DOM4-130-62 (SEQ ID NO:275), DOM4-130-63 (SEQ ID NO:276), DOM4-130-64 (SEQ ID NO:277), DOM4-130-65 (SEQ ID NO:278), DOM4-130-66 (SEQ ID NO:279), DOM4-130-67 (SEQ ID NO:280), DOM4-130-68 (SEQ ID NO:281), DOM4-130-69 (SEQ ID NO:282), DOM4-130-70 (SEQ ID NO:283), DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287), DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID NO:292), DOM4-130-80 (SEQ ID NO:293), DOM4-130-81 (SEQ ID NO:294), DOM4-130-82 (SEQ ID NO:295), DOM4-130-83 (SEQ ID NO:296), DOM4-130-84 (SEQ ID NO:297), DOM4-130-85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID NO:300), DOM4-130-88 (SEQ ID NO:301), DOM4-130-89 (SEQ ID NO:302), DOM4-130-90 (SEQ ID NO:303), DOM4-130-91 (SEQ ID NO:304), DOM4-130-92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID NO:307), DOM4-130-95 (SEQ ID NO:308), DOM4-130-96 (SEQ ID NO:309), DOM4-130-97 (SEQ ID NO:310), DOM4-130-98 (SEQ ID NO:311), DOM4-130-99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315), DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107

(SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324), DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

44. The use of claim 42, wherein said immunoglobulin single variable domain binds human serum albumin comprises an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID

NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55),

5 DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69),

10 DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110

15 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113 (SEQ ID NO:86), DOM4-114 (SEQ ID NO:87), DOM4-115 (SEQ ID NO:88), DOM4-116 (SEQ ID NO:89), DOM4-117 (SEQ ID NO:90), DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102), DOM4-122-8 (SEQ ID NO:103), DOM4-122-9 (SEQ ID NO:104), DOM4-122-10 (SEQ ID NO:105), DOM4-122-11 (SEQ ID NO:106), DOM4-122-12 (SEQ ID NO:107), DOM4-122-13 (SEQ ID NO:108), DOM4-122-14 (SEQ ID NO:109), DOM4-122-15 (SEQ ID NO:110), DOM4-122-16 (SEQ ID NO:111), DOM4-122-17 (SEQ ID NO:112), DOM4-122-18 (SEQ ID NO:113), DOM4-122-19 (SEQ ID NO:114), DOM4-122-20 (SEQ ID NO:115), DOM4-122-21 (SEQ ID NO:116), DOM4-122-22 (SEQ ID NO:117), DOM4-122-25 (SEQ ID NO:118), DOM4-122-26 (SEQ ID NO:119), DOM4-122-27 (SEQ ID NO:120), DOM4-122-28 (SEQ ID NO:121), DOM4-122-29 (SEQ ID NO:122), DOM4-122-30 (SEQ ID NO:123), DOM4-122-31 (SEQ ID NO:124), DOM4-122-32 (SEQ ID NO:125), DOM4-122-33 (SEQ ID NO:126), DOM4-122-

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45. The use of any one of claims 42-44, wherein said respiratory disease is selected from the group consisting of lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary
5 infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease,
10 lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax,
15 pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, sarcoidosis, and Wegener's granulomatosis.

20 46. The use of any one of claims 1-45 wherein said IL-1 is selected from the group consisting of IL-1 α and IL-1 β .

47. A pharmaceutical composition comprising an antagonist of IL-1R1 and a physiologically acceptable carrier, wherein said antagonist of IL-1R1 is as
25 described in any one of the previous claims.

48. A drug delivery device comprising the pharmaceutical composition of claims 47.

30 49. The drug deliver device of claim 48 wherein said drug delivery device is selected from the group consisting of a parenteral delivery device, intravenous delivery device, intramuscular delivery device, intraperitoneal delivery

device, transdermal delivery device, pulmonary delivery device, intraarterial delivery device, intrathecal delivery device, intraarticular delivery device, subcutaneous delivery device, intranasal delivery device, vaginal delivery device, and rectal delivery device.

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50. The drug delivery device of claim 49 wherein said device is selected from the group consisting of a syringe, a transdermal delivery device, a capsule, a tablet, a nebulizer, an inhaler, an atomizer, an aerosolizer, a mister, a dry powder inhaler, a metered dose inhaler, a metered dose sprayer, a metered dose mister, a metered dose atomizer, a catheter.

10

51. A method for treating a respiratory disease, comprising administering to a subject in need thereof a therapeutically effective amount of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1), wherein said antagonist of IL-1R1 comprises a polypeptide domain that has binding specificity for Interleukin-1 Receptor Type 1 (IL-1R1) and inhibits binding of Interleukin-1 (IL-1) to IL-1R1, and wherein said polypeptide domain that has binding specificity for IL-1R1 is selected from the group consisting of an antibody or antigen-binding fragment thereof, Interleukin-1 receptor antagonist (IL-1ra) or a functional variant of IL-1ra.

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20

52. The method of claim 51, wherein said polypeptide domain that has binding specificity for IL-1R1 inhibits binding of said ligand to IL-1R1 with an IC50 that is $\leq 1 \mu\text{M}$.

25

53. The method of claim 51, wherein said polypeptide domain that has binding specificity for IL-1R1 inhibits IL-1-induced release of Interleukin-8 by MRC-5 cells (ATCC Accession No. CCL-171) in an *in vitro* assay with a ND50 that is $\leq 1 \mu\text{M}$.

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54. The method of claim 53, wherein said polypeptide domain that has binding specificity for IL-1R1 inhibits IL-1-induced release of Interleukin-8 by

MRC-5 cells (ATCC Accession No. CCL-171) in an *in vitro* assay with a ND50 that is ≤ 1 nM.

55. The method of claim 51, wherein said polypeptide domain that has
5 binding specificity for IL-1R1 inhibits IL-1-induced release of Interleukin-6 in a whole blood assay with a ND50 that is ≤ 1 μ M.

56. The method of claim 51, wherein said polypeptide domain that has
binding specificity for IL-1R1 is an antigen-binding fragment of an antibody, and
10 said antigen-binding fragment is an immunoglobulin single variable domain.

57. The method of claim 56, wherein one or more of the framework
regions (FR) in said immunoglobulin single variable domain comprise (a) the amino
acid sequence of a human framework region, (b) at least 8 contiguous amino acids of
15 the amino acid sequence of a human framework region, or (c) an amino acid
sequence encoded by a human germline antibody gene segment, wherein said
framework regions are as defined by Kabat.

58. The method of claim 56, wherein the amino acid sequences of one or
20 more framework regions in said immunoglobulin single variable domain are the
same as the amino acid sequence of a corresponding framework region encoded by a
human germline antibody gene segment, or the amino acid sequences of one or more
of said framework regions collectively comprise up to 5 amino acid differences
relative to the corresponding framework regions encoded by a human germline
25 antibody gene segment.

59. The method of claim 56, wherein the amino acid sequences of FR1,
FR2, FR3 and FR4 in said immunoglobulin single variable domain are the same as
the amino acid sequences of corresponding framework regions encoded by a human
30 germline antibody gene segment, or the amino acid sequences of FR1, FR2, FR3 and
FR4 collectively contain up to 10 amino acid differences relative to the

corresponding framework regions encoded by a human germline antibody gene segment.

60. The method of claim 56, wherein the immunoglobulin single variable domain comprises FR1, FR2 and FR3 regions, and the amino acid sequence of said FR1, FR2 and FR3 are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment.

61. The method of any one of claims 57-60, wherein said human germline antibody gene segment comprises is DPK9 and JK1.

62. The method of claim 56, wherein said immunoglobulin single variable domain competes for binding to IL-1R1 with an immunoglobulin single variable domain selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51),

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70 (SEQ ID NO:283), DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287), DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID NO:292), DOM4-130-80 (SEQ ID NO:293), DOM4-130-81 (SEQ ID NO:294), DOM4-130-82 (SEQ ID NO:295), DOM4-130-83 (SEQ ID NO:296), DOM4-130-84 (SEQ ID NO:297), DOM4-130-85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID NO:300), DOM4-130-88 (SEQ ID NO:301), DOM4-130-89 (SEQ ID NO:302), DOM4-130-90 (SEQ ID NO:303), DOM4-130-91 (SEQ ID NO:304), DOM4-130-92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID NO:307), DOM4-130-95 (SEQ ID NO:308), DOM4-130-96 (SEQ ID NO:309), DOM4-130-97 (SEQ ID NO:310), DOM4-130-98 (SEQ ID NO:311), DOM4-130-99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315), DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107 (SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324), DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

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63. The method of claim 56, wherein said immunoglobulin single variable domain comprises an amino acid sequence that has at least about 90%

amino acid sequence identity with an amino acid sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7),

5 DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ

10 ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ

15 ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ

20 ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ

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30 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113

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(SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96),
5 DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4
(SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID
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15 27 (SEQ ID NO:120), DOM4-122-28 (SEQ ID NO:121), DOM4-122-29 (SEQ ID
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25 NO:143), DOM4-122-51 (SEQ ID NO:144), DOM4-122-52 (SEQ ID NO:145),
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30 63 (SEQ ID NO:155), DOM4-122-64 (SEQ ID NO:156), DOM4-122-65 (SEQ ID
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70 (SEQ ID NO:162), DOM4-122-71 (SEQ ID NO:163), DOM4-122-72 (SEQ ID NO:164), DOM4-122-73 (SEQ ID NO:165), DOM4-123 (SEQ ID NO:166), DOM4-124 (SEQ ID NO:167) DOM4-125 (SEQ ID NO:168), DOM4-126 (SEQ ID NO:169), DOM4-127 (SEQ ID NO:170), DOM4-128 (SEQ ID NO:171), DOM4-129 (SEQ ID NO:172), DOM4-129-1 (SEQ ID NO:173,) DOM4-129-2 (SEQ ID NO:174), DOM4-129-3 (SEQ ID NO:175), DOM4-129-4 (SEQ ID NO:176), DOM4-129-5 (SEQ ID NO:177), DOM4-129-6 (SEQ ID NO:178), DOM4-129-7 (SEQ ID NO:179), DOM4-129-8 (SEQ ID NO:180), DOM4-129-9 (SEQ ID NO:181), DOM4-129-10 (SEQ ID NO:182), DOM4-129-11 (SEQ ID NO:183), DOM4-129-12 (SEQ ID NO:184), DOM4-129-13 (SEQ ID NO:185), DOM4-129-14 (SEQ ID NO:186), DOM4-129-15 (SEQ ID NO:187), DOM4-129-16 (SEQ ID NO:188), DOM4-129-17 (SEQ ID NO:189), DOM4-129-18 (SEQ ID NO:190), DOM4-129-19 (SEQ ID NO:191), DOM4-129-20 (SEQ ID NO:192), DOM4-129-21 (SEQ ID NO:193), DOM4-129-22 (SEQ ID NO:194), DOM4-129-23 (SEQ ID NO:195), DOM4-129-24 (SEQ ID NO:196), DOM4-129-25 (SEQ ID NO:197), DOM4-129-26 (SEQ ID NO:198), DOM4-129-27 (SEQ ID NO:199), DOM4-129-28 (SEQ ID NO:200), DOM4-129-29 (SEQ ID NO:201), DOM4-129-31 (SEQ ID NO:202), DOM4-129-32 (SEQ ID NO:203), DOM4-129-33 (SEQ ID NO:204), DOM4-129-34 (SEQ ID NO:205), DOM4-129-35 (SEQ ID NO:206), DOM4-129-37 (SEQ ID NO:207), DOM4-129-38 (SEQ ID NO:208), DOM4-129-39 (SEQ ID NO:209), DOM4-129-40 (SEQ ID NO:210), DOM4-129-41 (SEQ ID NO:211), DOM4-129-42 (SEQ ID NO:212), DOM4-129-43 (SEQ ID NO:213), DOM4-129-44 (SEQ ID NO:214), DOM4-130 (SEQ ID NO:215), DOM4-130-1 (SEQ ID NO:216), DOM4-130-2 (SEQ ID NO:217), DOM4-130-3 (SEQ ID NO:218), DOM4-130-4 (SEQ ID NO:219), DOM4-130-5 (SEQ ID NO:220), DOM4-130-6 (SEQ ID NO:221), DOM4-130-7 (SEQ ID NO:222), DOM4-130-8 (SEQ ID NO:223), DOM4-130-9 (SEQ ID NO:224), DOM4-130-10 (SEQ ID NO:225), DOM4-130-11 (SEQ ID NO:226), DOM4-130-12 (SEQ ID NO:227), DOM4-130-13 (SEQ ID NO:228), DOM4-130-14 (SEQ ID NO:229), DOM4-130-15 (SEQ ID NO:230), DOM4-130-16 (SEQ ID NO:231), DOM4-130-17 (SEQ ID NO:232), DOM4-130-18 (SEQ ID NO:233), DOM4-130-19 (SEQ ID NO:234), DOM4-130-20 (SEQ ID NO:235), DOM4-130-21 (SEQ ID NO:236), DOM4-130-22 (SEQ ID

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36 (SEQ ID NO:249), DOM4-130-37 (SEQ ID NO:250), DOM4-130-38 (SEQ ID
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85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID
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30 92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID
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99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315), DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107 (SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324), DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

64. The method of claim 51, wherein said polypeptide domain that has binding specificity for IL-1R1 binds human IL-1R1 with an affinity (KD) of about 300 nM to about 5 pM, as determined by surface plasmon resonance.

65. The method of claim 51, wherein said antagonist of IL-1R1 further comprises a half-life extending moiety.

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66. The method of claim 65, wherein said half-life extending moiety is a polyalkylene glycol moiety, serum albumin or a fragment thereof, transferrin receptor or a transferrin-binding portion thereof, or an antibody or antibody fragment comprising a binding site for a polypeptide that enhances half-life *in vivo*.

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67. The method of claim 66, wherein said half-life extending moiety is a polyethylene glycol moiety.

68. The method of claim 66, wherein said half-life extending moiety is an antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc receptor.

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69. The method of claim 68, wherein said antibody or antibody fragment is an antibody fragment, and said antibody fragment is an immunoglobulin single variable domain.

10 70. The method of claim 69, wherein said immunoglobulin single variable domain competes with an immunoglobulin single variable domain selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729),
15 DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-
20 21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K

(SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784), for binding to human serum albumin.

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71. The method of claim 69, wherein said immunoglobulin single variable domain binds human serum albumin comprises an amino acid sequence selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726),
- 10 DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-
- 15 24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20
- 20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID
- 25 NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ
- 30 ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784).

72. The method of claim 51, wherein said antagonist of IL-1R1 further comprises a polypeptide binding domain that has binding specificity for Tumor Necrosis Factor Receptor 1 (TNFR1, p55) and inhibits binding of Tumor Necrosis Factor Alpha (TNF α) to TNFR1.

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73. The method of claim 51, wherein said antagonist of IL-1R1 binds human IL-1R1 with an affinity (KD) of about 300 nM to about 5 pM, as determined by surface plasmon resonance.

10 74. The method of claim 51, wherein said respiratory disease is selected from the group consisting of lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary
15 thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic
20 pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary
25 tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, sarcoidosis, and Wegener's granulomatosis.

75. The method of claim 51, further comprising administering to said subject a therapeutically effective amount of an antagonist of Tumor Necrosis Factor
30 Receptor 1 (TNFR1, p55).

76. The method of claim 51, wherein said antagonist of IL-1R1 is administered systemically.
77. The method of claim 76, wherein said antagonist of IL-1R1 is administered intraperitoneally or subcutaneously.
78. The method of claim 51, wherein said antagonist of IL-1R1 is locally administered to pulmonary tissue.
79. The method of claim 78, wherein said antagonist of IL-1R1 is administered by inhalation or intranasal administration.
80. The method of claim 51, wherein the level of inflammatory cells in the lung is assessed by total cell counts in bronchoalveolar lavage, sputum or bronchial biopsy is reduced relative to pretreatment levels.
81. The method of claim 80, wherein the level of inflammatory cells in the lung is assessed by macrophage, polymorphonuclear, lymphocyte and/or eosinophil cell counts in bronchoalveolar lavage, sputum or bronchial biopsy.
82. A method for treating a respiratory disease, comprising administering to a subject in need thereof a therapeutically effective amount of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1), wherein said antagonist of IL-1R1 is a fusion protein or a conjugate comprising an antagonist of IL-1R1 moiety and a half-life extending moiety, wherein said antagonist of IL-1R1 moiety binds human IL-1R1 and inhibits binding of Interleukin-1 (IL-1) to human IL-1R1, and said half-life extending moiety is a polypeptide binding moiety that contains a binding site with binding specificity for a polypeptide that enhances serum half-life *in vivo*.
83. The method of claim 82, wherein said antagonist of IL-1R1 moiety is human Interleukin 1 receptor antagonist (IL-1ra) or a functional variant of human IL-1ra.

84. The method of claim 82, wherein said antagonist of IL-1R1 moiety is an immunoglobulin single variable domain that competes for binding to IL-1R1 with a dAb selected from the group consisting of DOM4-122-23 (SEQ ID NO:1),
5 DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID

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 130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ
 ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

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85. The method of claim 82, wherein said antagonist of IL-1R1 moiety is
 an immunoglobulin single variable domain that comprises an amino acid sequence
 that has at least about 90% amino acid sequence identity with an amino acid
 sequence selected from the group consisting of DOM4-122-23 (SEQ ID NO:1),
 25 DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46
 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID
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5 DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

86. The method of claim 82, said half-life extending moiety is serum
10 albumin or a fragment thereof, transferrin receptor or a transferrin-binding portion thereof, or an antibody or antibody fragment comprising a binding site for a polypeptide that enhances half-life *in vivo*.

87. The method of claim 82, wherein said half-life extending moiety is an
15 antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc receptor.

88. The method of claim 87, wherein said antibody or antibody fragment
20 is an antibody fragment, and said antibody fragment is an immunoglobulin single variable domain.

89. The method of claim 88, wherein said immunoglobulin single
variable domain competes with an immunoglobulin single variable domain selected
from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID
25 NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737),
30 DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746),

DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756), DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784) for binding to human serum albumin.

90. The method of claim 88, wherein said immunoglobulin single variable domain binds human serum albumin comprises an amino acid sequence selected from the group consisting of DOM7m-16 (SEQ ID NO:723), DOM7m-12 (SEQ ID NO:724), DOM7m-26 (SEQ ID NO:725), DOM7r-1 (SEQ ID NO:726), DOM7r-3 (SEQ ID NO:727), DOM7r-4 (SEQ ID NO:728), DOM7r-5 (SEQ ID NO:729), DOM7r-7 (SEQ ID NO:730), DOM7r-8 (SEQ ID NO:731), DOM7h-2 (SEQ ID NO:732), DOM7h-3 (SEQ ID NO:733), DOM7h-4 (SEQ ID NO:734), DOM7h-6 (SEQ ID NO:735), DOM7h-1 (SEQ ID NO:736), DOM7h-7 (SEQ ID NO:737), DOM7h-22 (SEQ ID NO:739), DOM7h-23 (SEQ ID NO:740), DOM7h-24 (SEQ ID NO:741), DOM7h-25 (SEQ ID NO:742), DOM7h-26 (SEQ ID NO:743), DOM7h-21 (SEQ ID NO:744), DOM7h-27 (SEQ ID NO:745), DOM7h-8 (SEQ ID NO:746), DOM7r-13 (SEQ ID NO:747), DOM7r-14 (SEQ ID NO:748), DOM7r-15 (SEQ ID NO:749), DOM7r-16 (SEQ ID NO:750), DOM7r-17 (SEQ ID NO:751), DOM7r-18 (SEQ ID NO:752), DOM7r-19 (SEQ ID NO:753), DOM7r-20 (SEQ ID NO:754), DOM7r-21 (SEQ ID NO:755), DOM7r-22 (SEQ ID NO:756),

DOM7r-23 (SEQ ID NO:757), DOM7r-24 (SEQ ID NO:758), DOM7r-25 (SEQ ID NO:759), DOM7r-26 (SEQ ID NO:760), DOM7r-27 (SEQ ID NO:761), DOM7r-28 (SEQ ID NO:762), DOM7r-29 (SEQ ID NO:763), DOM7r-30 (SEQ ID NO:764), DOM7r-31 (SEQ ID NO:765), DOM7r-32 (SEQ ID NO:766), DOM7r-33 (SEQ ID NO:767), Sequence A (SEQ ID NO:768), Sequence B (SEQ ID NO:769), Sequence C (SEQ ID NO:770), Sequence D (SEQ ID NO:771), Sequence E (SEQ ID NO:772), Sequence F (SEQ ID NO:773), Sequence G (SEQ ID NO:774), Sequence H (SEQ ID NO:775), Sequence I (SEQ ID NO:776), Sequence J (SEQ ID NO:777), Sequence K (SEQ ID NO:778), Sequence L (SEQ ID NO:779), Sequence M (SEQ ID NO:780), Sequence N (SEQ ID NO:781), Sequence O (SEQ ID NO:782), Sequence P (SEQ ID NO:783), and Sequence Q (SEQ ID NO:784).

91. The method of claim 82, wherein said respiratory disease is selected from the group consisting of lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, sarcoidosis, and Wegener's granulomatosis.

92. A method for treating a respiratory disease, comprising administering to a subject in need thereof a therapeutically effective amount of an antagonist of Interleukin-1 Receptor Type 1 (IL-1R1), wherein said antagonist of IL-1R1

comprises an immunoglobulin single variable domain that has binding specificity for human IL-1R1 and inhibits binding of Interleukin-1 (IL-1) to human IL-1R1, and a polyethylene glycol moiety.

- 5 93. The method of claim 92, wherein said immunoglobulin single variable domain competes for binding to human IL-1R1 with a dAb selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4), DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54 (SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6 (SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9 (SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18), DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID

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DOM4-130-11 (SEQ ID NO:226), DOM4-130-12 (SEQ ID NO:227), DOM4-130-13 (SEQ ID NO:228), DOM4-130-14 (SEQ ID NO:229), DOM4-130-15 (SEQ ID NO:230), DOM4-130-16 (SEQ ID NO:231), DOM4-130-17 (SEQ ID NO:232), DOM4-130-18 (SEQ ID NO:233), DOM4-130-19 (SEQ ID NO:234), DOM4-130-20 (SEQ ID NO:235), DOM4-130-21 (SEQ ID NO:236), DOM4-130-22 (SEQ ID NO:237), DOM4-130-23 (SEQ ID NO:238), DOM4-130-24 (SEQ ID NO:239), DOM4-130-25 (SEQ ID NO:240), DOM4-130-26 (SEQ ID NO:241), DOM4-130-27 (SEQ ID NO:242), DOM4-130-28 (SEQ ID NO:243), DOM4-130-31 (SEQ ID NO:244), DOM4-130-32 (SEQ ID NO:245), DOM4-130-33 (SEQ ID NO:246), DOM4-130-34 (SEQ ID NO:247), DOM4-130-35 (SEQ ID NO:248), DOM4-130-36 (SEQ ID NO:249), DOM4-130-37 (SEQ ID NO:250), DOM4-130-38 (SEQ ID NO:251), DOM4-130-39 (SEQ ID NO:252), DOM4-130-40 (SEQ ID NO:253), DOM4-130-41 (SEQ ID NO:254), DOM4-130-42 (SEQ ID NO:255), DOM4-130-43 (SEQ ID NO:256), DOM4-130-44 (SEQ ID NO:257), DOM4-130-45 (SEQ ID NO:258), DOM4-130-46 (SEQ ID NO:259), DOM4-130-47 (SEQ ID NO:260), DOM4-130-48 (SEQ ID NO:261), DOM4-130-49 (SEQ ID NO:262), DOM4-130-50 (SEQ ID NO:263), DOM4-130-51 (SEQ ID NO:264), DOM4-130-52 (SEQ ID NO:265), DOM4-130-53 (SEQ ID NO:266), DOM4-130-54 (SEQ ID NO:267), DOM4-130-55 (SEQ ID NO:268), DOM4-130-56 (SEQ ID NO:269), DOM4-130-57 (SEQ ID NO:270), DOM4-130-58 (SEQ ID NO:271), DOM4-130-59 (SEQ ID NO:272), DOM4-130-60 (SEQ ID NO:273), DOM4-130-61 (SEQ ID NO:274), DOM4-130-62 (SEQ ID NO:275), DOM4-130-63 (SEQ ID NO:276), DOM4-130-64 (SEQ ID NO:277), DOM4-130-65 (SEQ ID NO:278), DOM4-130-66 (SEQ ID NO:279), DOM4-130-67 (SEQ ID NO:280), DOM4-130-68 (SEQ ID NO:281), DOM4-130-69 (SEQ ID NO:282), DOM4-130-70 (SEQ ID NO:283), DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287), DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID NO:292), DOM4-130-80 (SEQ ID NO:293), DOM4-130-81 (SEQ ID NO:294), DOM4-130-82 (SEQ ID NO:295), DOM4-130-83 (SEQ ID NO:296), DOM4-130-84 (SEQ ID NO:297), DOM4-130-85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID

NO:300), DOM4-130-88 (SEQ ID NO:301), DOM4-130-89 (SEQ ID NO:302),
DOM4-130-90 (SEQ ID NO:303), DOM4-130-91 (SEQ ID NO:304), DOM4-130-
92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID
NO:307), DOM4-130-95 (SEQ ID NO:308), DOM4-130-96 (SEQ ID NO:309),
5 DOM4-130-97 (SEQ ID NO:310), DOM4-130-98 (SEQ ID NO:311), DOM4-130-
99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID
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DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-
130-106 (SEQ ID NO:319), DOM4-130-107 (SEQ ID NO:320), DOM4-130-108
10 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID
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DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-
130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329), DOM4-130-117
(SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID
15 NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334),
DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-
130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338), DOM4-130-126
(SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID
NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343),
20 DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-
130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID
NO:348), and DOM4-133 (SEQ ID NO:349).

94. The method of claim 92, wherein said immunoglobulin single
25 variable domain binds human serum albumin comprises an amino acid sequence
selected from the group consisting of DOM4-122-23 (SEQ ID NO:1), DOM4-122-
24 (SEQ ID NO:2), DOM4-130-30 (SEQ ID NO:3), DOM4-130-46 (SEQ ID NO:4),
DOM4-130-51 (SEQ ID NO:5), DOM4-130-53 (SEQ ID NO:6), DOM4-130-54
(SEQ ID NO:7), DOM4-1 (SEQ ID NO:8), DOM4-2 (SEQ ID NO:9), DOM4-3
30 (SEQ ID NO:10), DOM4-4 (SEQ ID NO:11), DOM4-5 (SEQ ID NO:12), DOM4-6
(SEQ ID NO:13), DOM4-7 (SEQ ID NO:14), DOM4-8 (SEQ ID NO:15), DOM4-9
(SEQ ID NO:16), DOM4-10 (SEQ ID NO:17), DOM4-11 (SEQ ID NO:18),

DOM4-12 (SEQ ID NO:19), DOM4-13 (SEQ ID NO:20), DOM4-14 (SEQ ID NO:21), DOM4-15 (SEQ ID NO:22), DOM4-20 (SEQ ID NO:23), DOM4-21 (SEQ ID NO:24), DOM4-22 (SEQ ID NO:25), DOM4-23 (SEQ ID NO:26), DOM4-25 (SEQ ID NO:27), DOM4-26 (SEQ ID NO:28), DOM4-27 (SEQ ID NO:29), DOM4-28 (SEQ ID NO:30), DOM4-29 (SEQ ID NO:31), DOM4-31 (SEQ ID NO:32), DOM4-32 (SEQ ID NO:33), DOM4-33 (SEQ ID NO:34), DOM4-34 (SEQ ID NO:35), DOM4-36 (SEQ ID NO:36), DOM4-37 (SEQ ID NO:37), DOM4-38 (SEQ ID NO:38), DOM4-39 (SEQ ID NO:39), DOM4-40 (SEQ ID NO:40), DOM4-41 (SEQ ID NO:41), DOM4-42 (SEQ ID NO:42), DOM4-44 (SEQ ID NO:43), DOM4-45 (SEQ ID NO:44), DOM4-46 (SEQ ID NO:45), DOM4-49 (SEQ ID NO:46), DOM4-50 (SEQ ID NO:47), DOM4-74 (SEQ ID NO:48), DOM4-75 (SEQ ID NO:49), DOM4-76 (SEQ ID NO:50), DOM4-78 (SEQ ID NO:51), DOM4-79 (SEQ ID NO:52), DOM4-80 (SEQ ID NO:53), DOM4-81 (SEQ ID NO:54), DOM4-82 (SEQ ID NO:55), DOM4-83 (SEQ ID NO:56), DOM4-84 (SEQ ID NO:57), DOM4-85 (SEQ ID NO:58), DOM4-86 (SEQ ID NO:59), DOM4-87 (SEQ ID NO:60), DOM4-88 (SEQ ID NO:61), DOM4-89 (SEQ ID NO:62), DOM4-90 (SEQ ID NO:63), DOM4-91 (SEQ ID NO:64), DOM4-92 (SEQ ID NO:65), DOM4-93 (SEQ ID NO:66), DOM4-94 (SEQ ID NO:67), DOM4-95 (SEQ ID NO:68), DOM4-96 (SEQ ID NO:69), DOM4-97 (SEQ ID NO:70), DOM4-98 (SEQ ID NO:71), DOM4-99 (SEQ ID NO:72), DOM4-100 (SEQ ID NO:73), DOM4-101 (SEQ ID NO:74), DOM4-102 (SEQ ID NO:75), DOM4-103 (SEQ ID NO:76), DOM4-104 (SEQ ID NO:77), DOM4-105 (SEQ ID NO:78), DOM4-106 (SEQ ID NO:79), DOM4-107 (SEQ ID NO:80), DOM4-108 (SEQ ID NO:81), DOM4-109 (SEQ ID NO:82), DOM4-110 (SEQ ID NO:83), DOM4-111 (SEQ ID NO:84), DOM4-112 (SEQ ID NO:85), DOM4-113 (SEQ ID NO:86), DOM4-114 (SEQ ID NO:87), DOM4-115 (SEQ ID NO:88), DOM4-116 (SEQ ID NO:89), DOM4-117 (SEQ ID NO:90), DOM4-118 (SEQ ID NO:91), DOM4-119 (SEQ ID NO:92), DOM4-120 (SEQ ID NO:93), DOM4-121 (SEQ ID NO:94), DOM4-122 (SEQ ID NO:95), DOM4-122-1 (SEQ ID NO:96), DOM4-122-2 (SEQ ID NO:97), DOM4-122-3 (SEQ ID NO:98), DOM4-122-4 (SEQ ID NO:99), DOM4-122-5 (SEQ ID NO:100), DOM4-122-6 (SEQ ID NO:101), DOM4-122-7 (SEQ ID NO:102), DOM4-122-8 (SEQ ID NO:103), DOM4-122-9 (SEQ ID NO:104), DOM4-122-10 (SEQ ID NO:105),

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DOM4-130-43(SEQ ID NO:256), DOM4-130-44(SEQ ID NO:257), DOM4-130-45(SEQ ID NO:258), DOM4-130-46(SEQ ID NO:259), DOM4-130-47 (SEQ ID NO:260), DOM4-130-48 (SEQ ID NO:261), DOM4-130-49 (SEQ ID NO:262), DOM4-130-50 (SEQ ID NO:263), DOM4-130-51 (SEQ ID NO:264), DOM4-130-52 (SEQ ID NO:265), DOM4-130-53 (SEQ ID NO:266), DOM4-130-54 (SEQ ID NO:267), DOM4-130-55 (SEQ ID NO:268), DOM4-130-56 (SEQ ID NO:269), DOM4-130-57 (SEQ ID NO:270), DOM4-130-58 (SEQ ID NO:271), DOM4-130-59 (SEQ ID NO:272), DOM4-130-60 (SEQ ID NO:273), DOM4-130-61 (SEQ ID NO:274), DOM4-130-62 (SEQ ID NO:275), DOM4-130-63 (SEQ ID NO:276), DOM4-130-64 (SEQ ID NO:277), DOM4-130-65 (SEQ ID NO:278), DOM4-130-66 (SEQ ID NO:279), DOM4-130-67 (SEQ ID NO:280), DOM4-130-68 (SEQ ID NO:281), DOM4-130-69 (SEQ ID NO:282), DOM4-130-70 (SEQ ID NO:283), DOM4-130-71 (SEQ ID NO:284), DOM4-130-72 (SEQ ID NO:285), DOM4-130-73 (SEQ ID NO:286), DOM4-130-74 (SEQ ID NO:287), DOM4-130-75 (SEQ ID NO:288), DOM4-130-76 (SEQ ID NO:289), DOM4-130-77 (SEQ ID NO:290), DOM4-130-78 (SEQ ID NO:291), DOM4-130-79 (SEQ ID NO:292), DOM4-130-80 (SEQ ID NO:293), DOM4-130-81 (SEQ ID NO:294), DOM4-130-82 (SEQ ID NO:295), DOM4-130-83 (SEQ ID NO:296), DOM4-130-84 (SEQ ID NO:297), DOM4-130-85 (SEQ ID NO:298), DOM4-130-86 (SEQ ID NO:299), DOM4-130-87 (SEQ ID NO:300), DOM4-130-88 (SEQ ID NO:301), DOM4-130-89 (SEQ ID NO:302), DOM4-130-90 (SEQ ID NO:303), DOM4-130-91 (SEQ ID NO:304), DOM4-130-92 (SEQ ID NO:305), DOM4-130-93 (SEQ ID NO:306), DOM4-130-94 (SEQ ID NO:307), DOM4-130-95 (SEQ ID NO:308), DOM4-130-96 (SEQ ID NO:309), DOM4-130-97 (SEQ ID NO:310), DOM4-130-98 (SEQ ID NO:311), DOM4-130-99 (SEQ ID NO:312), DOM4-130-100 (SEQ ID NO:313), DOM4-130-101 (SEQ ID NO:314), DOM4-130-102 (SEQ ID NO:315), DOM4-130-103 (SEQ ID NO:316), DOM4-130-104 (SEQ ID NO:317), DOM4-130-105 (SEQ ID NO:318), DOM4-130-106 (SEQ ID NO:319), DOM4-130-107 (SEQ ID NO:320), DOM4-130-108 (SEQ ID NO:321), DOM4-130-109 (SEQ ID NO:322), DOM4-130-110 (SEQ ID NO:323), DOM4-130-111 (SEQ ID NO:324), DOM4-130-112 (SEQ ID NO:325), DOM4-130-113 (SEQ ID NO:326), DOM4-130-114 (SEQ ID NO:327), DOM4-130-115 (SEQ ID NO:328), DOM4-130-116 (SEQ ID NO:329),

DOM4-130-117 (SEQ ID NO:330), DOM4-130-118 (SEQ ID NO:331), DOM4-130-119 (SEQ ID NO:332), DOM4-130-120 (SEQ ID NO:333), DOM4-130-121 (SEQ ID NO:334), DOM4-130-122 (SEQ ID NO:335), DOM4-130-123 (SEQ ID NO:336), DOM4-130-124 (SEQ ID NO:337), DOM4-130-125 (SEQ ID NO:338),
5 DOM4-130-126 (SEQ ID NO:339), DOM4-130-127 (SEQ ID NO:340), DOM4-130-128 (SEQ ID NO:341), DOM4-130-129 (SEQ ID NO:342), DOM4-130-130 (SEQ ID NO:343), DOM4-130-131 (SEQ ID NO:344), DOM4-130-132 (SEQ ID NO:345), DOM4-130-133 (SEQ ID NO:346), DOM4-131 (SEQ ID NO:347), DOM4-132 (SEQ ID NO:348), and DOM4-133 (SEQ ID NO:349).

10

95. The method of claim 92, wherein said respiratory disease is selected from the group consisting of lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis, pulmonary infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis,
15 interstitial lung disease, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, asbestosis, aspergilloma, aspergillosis,
20 bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic pulmonary fibrosis, invasive pneumococcal disease, influenza, nontuberculous mycobacteria, pleural effusion, pneumoconiosis, pneumocytosis, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary inflammation, pulmonary
25 histiocytosis X, pulmonary hypertension, pulmonary nocardiosis, pulmonary tuberculosis, pulmonary veno-occlusive disease, rheumatoid lung disease, sarcoidosis, and Wegener's granulomatosis.

1/93

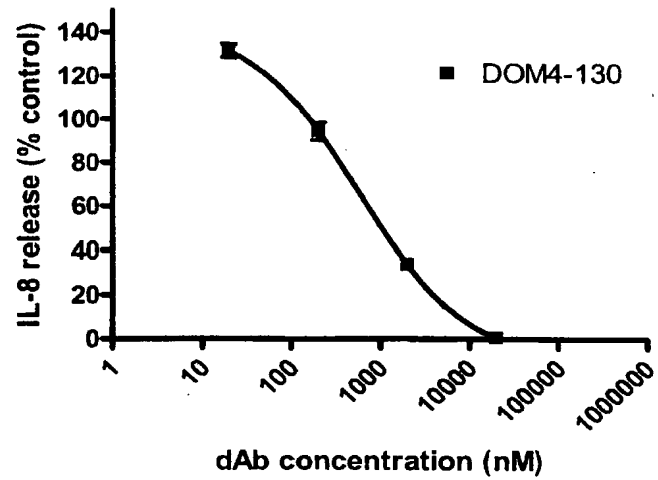


FIG. 1A

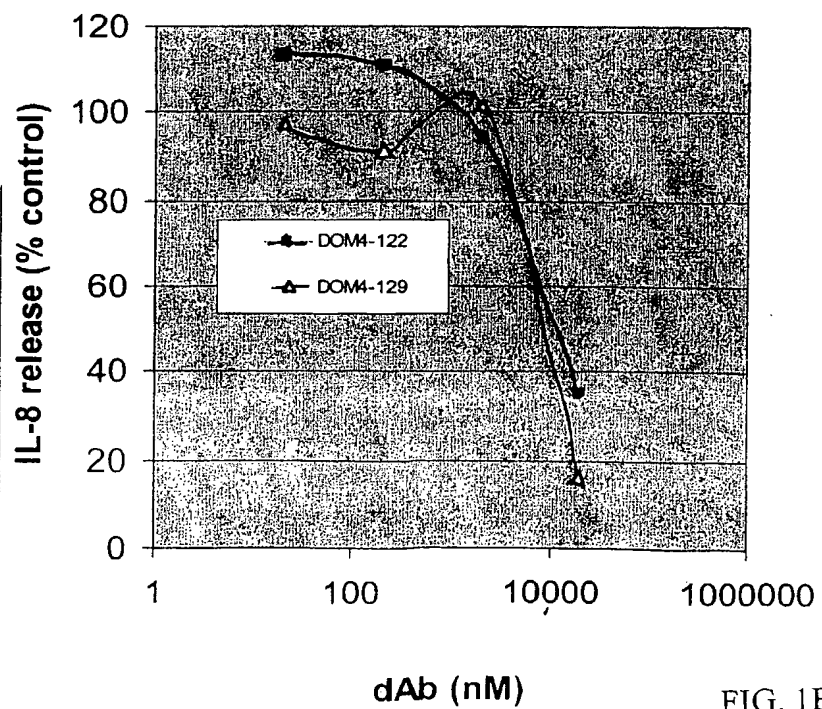


FIG. 1B

2/93

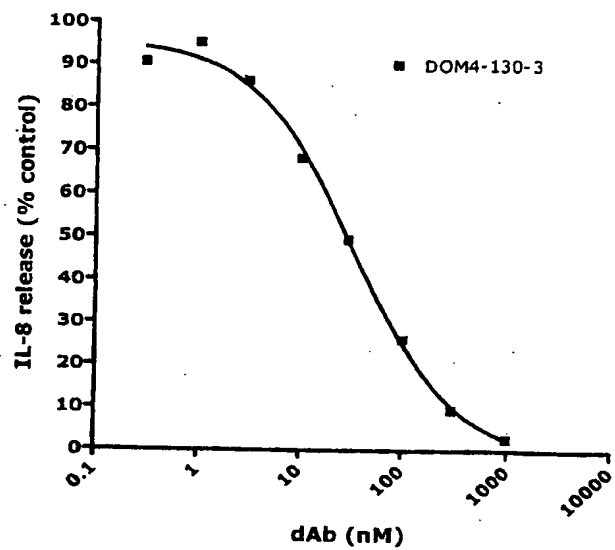


FIG. 2A

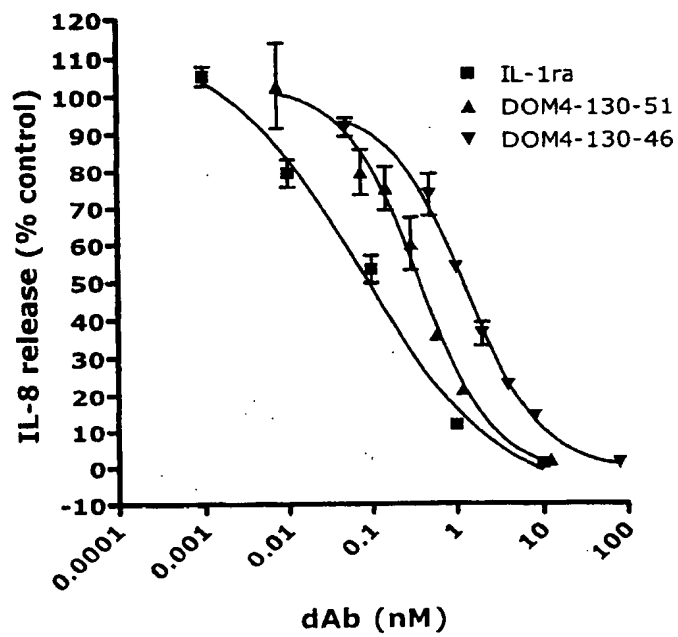


FIG. 2B

3/93

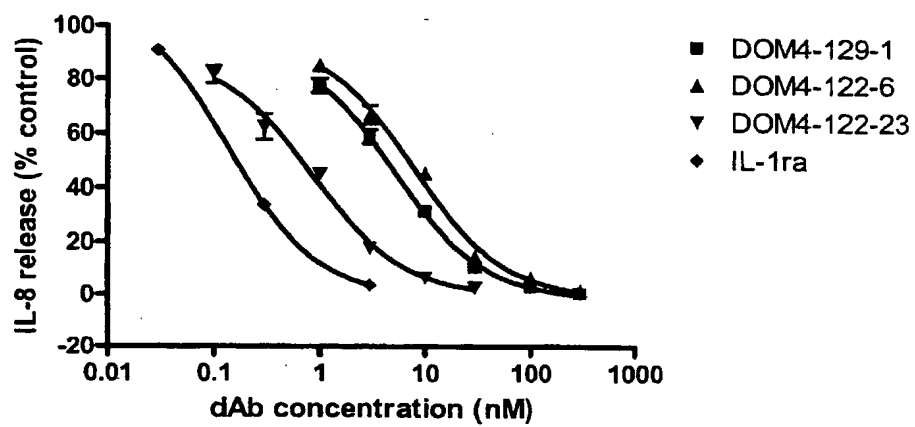


FIG. 3

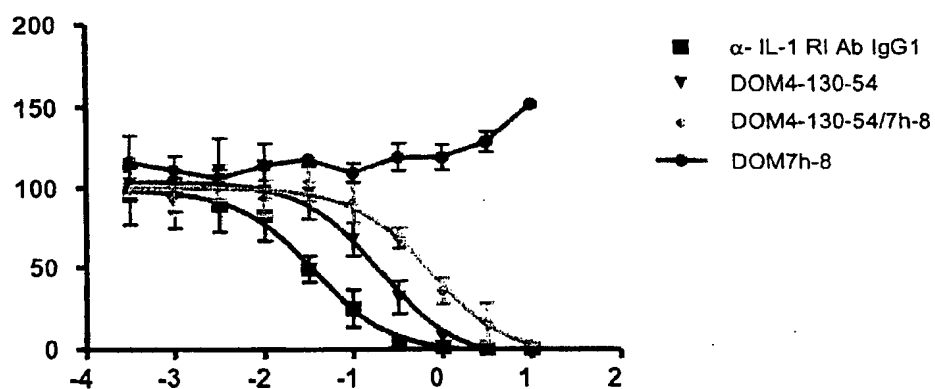


FIG. 4

4/93

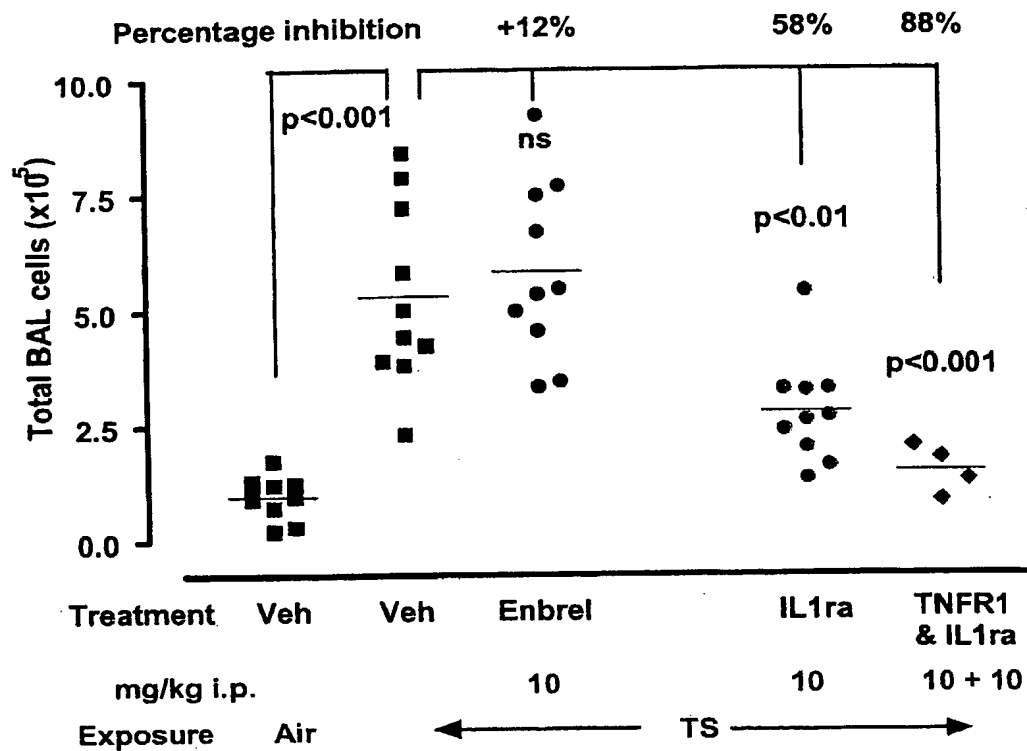


FIG. 5

dAb levels in BAL

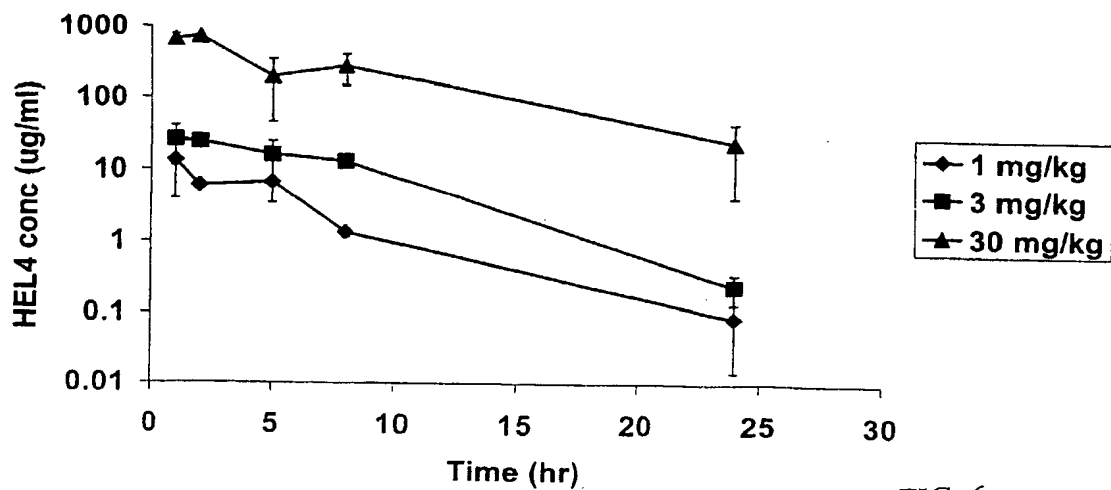


FIG. 6

5/93

dAb levels in serum

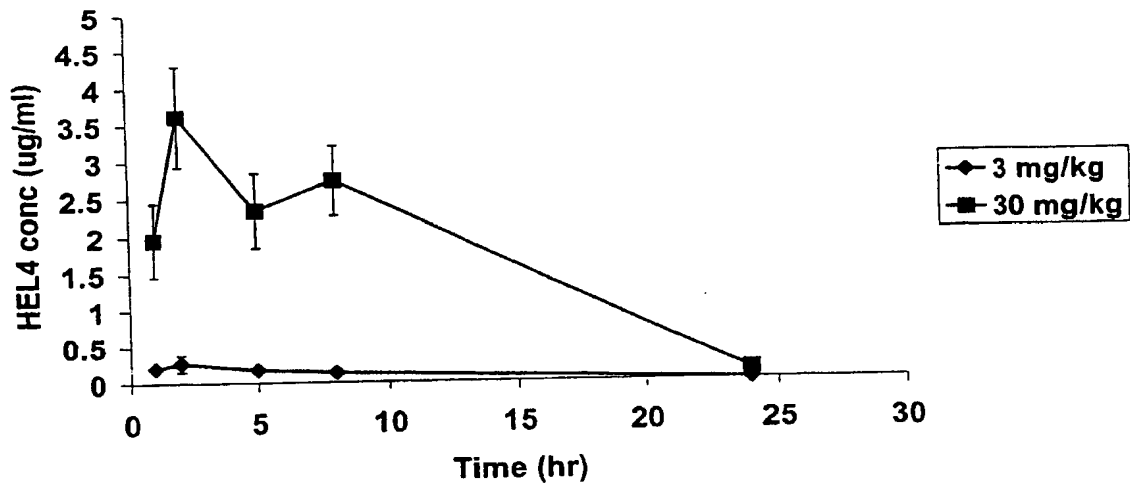


FIG. 7

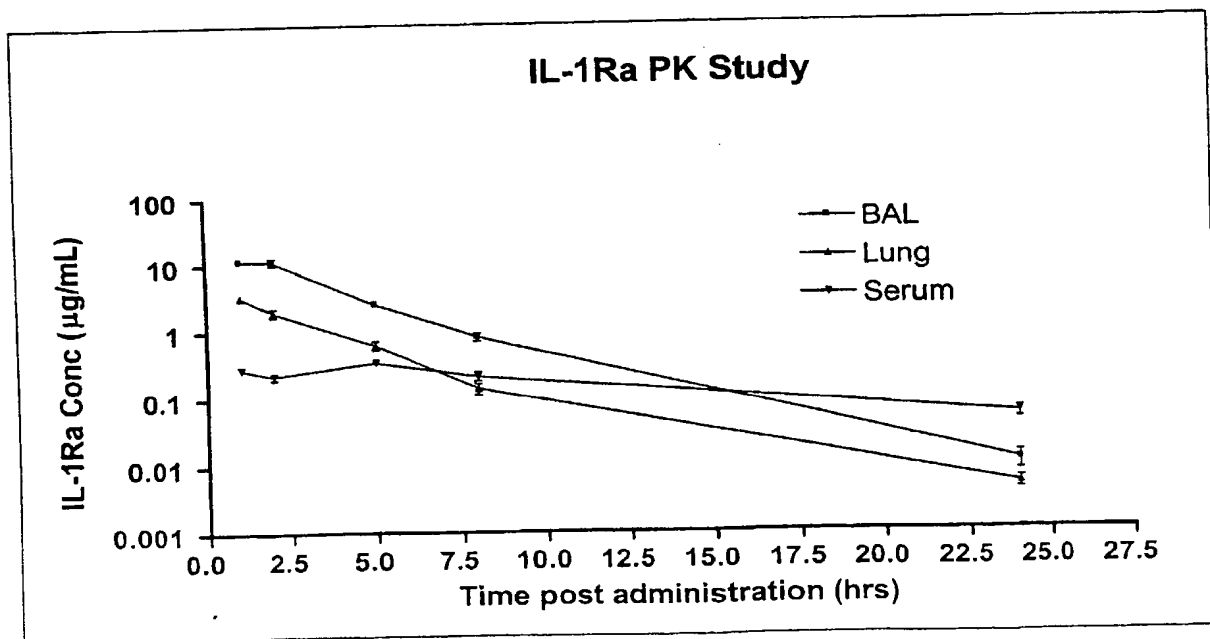


FIG. 8

6/93

>DOM4-122-23 (SEQ ID NO:1)
DIQMTQSPSSLSASVGDRTTITCRASQWIGRELRWYQQKPGKAPMFLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWPLTFGQGTKVEIKR

>DOM4-122-24 (SEQ ID NO:2)
DIQMTQSPSSLSASVGDRTTITCRASQWIGRELRWYQQKPGKAPFLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWPLTFGQGTKVEIKR

>DOM4-130-30 (SEQ ID NO:3)
DIQMTQSPSSLSASVGDRTTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSDLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-46 (SEQ ID NO:4)
DIQMTQSPSSLSASVGDRTTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-51 (SEQ ID NO:5)
DIQMTQSPSSLSASVGDRTTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-53 (SEQ ID NO:6)
DIQMTQSPSSLSASVGDRTTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-54 (SEQ ID NO:7)
DIQMTQSPSSLSASVGDRTTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-1 (SEQ ID NO:8)
DIQMTQSPSSLSASVGDRTTITCRASQSIYYFLHWYQQKPGKAPKLLIYRASSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQVWRPPLTFGQGTKVEIKR

>DOM4-2 (SEQ ID NO:9)
DIQMTQSPSSLSASVGDRTTITCRASQSIYQSLDWYQQKPGKAPKLLIYYASVLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQLSRPPFTFGQGTKVEIKR

>DOM4-3 (SEQ ID NO:10)
DIQMTQSPSSLSASVGDRTTITCRASQSIEMLYWYQQKPGKAPKLLIYNASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCRQVVGTPHTFGQGTKVEIKR

>DOM4-4 (SEQ ID NO:11)
DIQMTQSPSSLSASVGDRTTITCRASQSIDYLNWYQQKPGKAPKLLIYWASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQRWLTPTFGQGTKVEIKR

>DOM4-5 (SEQ ID NO:12)
DIQMTQSPSSLSASVGDRTTITCRASQSIEMLYWYQQKPGKAPKLLIYNASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCRQVVGTPHTFGQGTKVEIKR

>DOM4-6 (SEQ ID NO:13)
DIQMTQSPSSLSASVGDRTTITCRASQSIDYLNWYQQKPGKAPKLLIYWASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQKWMGPHTFGQGTKVEIKR

>DOM4-7 (SEQ ID NO:14)
DIQMTQSPSSLSASVGDRTTITCRASQNIDWGLDWYQQKPGKAPKLLIYMASRLQSGVPS

FIG. 9A

7/93

RFSGSGSGTDFTLTISLQPEDFATYYCQQLSMWPFTFGQGTKVEIKR

>DOM4-8 (SEQ ID NO:15)

DIQMTQSPSSLSASVGDRVTITCRASQSILDYLSWYQQKPGKAPKLLIYWASKLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQKWMGPHTFGQGTKVEIKR

>DOM4-9 (SEQ ID NO:16)

DIQMTQSPSSLSASVGDRVTITCRASQSISEYLYWYQQKPGKAPKLLIYHASTLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCRQYLRPPLTFGQGTKVEIKR

>DOM4-10 (SEQ ID NO:17)

DIQMTQSPSSLSASVGDRVTITCRASQWIGVSLNWWYQQKPGKAPKLLIYQSSLLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQVYIFPFTFGQGTKVEIKR

>DOM4-11 (SEQ ID NO:18)

DIQMTQSPSSLSASVGDRVTITCRASQPIERWLYWYQQKPGKAPKLLIYGASELQSGVPS
RFSGRSGTDFTLTISLQPEDFATYYCQYHAYPFTFGQGTKVEIKR

>DOM4-12 (SEQ ID NO:19)

DIQMTQSPSSLSASVGDRVTITCRASQNIWYLNWYQQKPGKAPKLLIYGSSLLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQDWSPPFTFGQGTKVEIKR

>DOM4-13 (SEQ ID NO:20)

DIQMTQSPSFLSASVGDRVTITCRASQVIGITLNWYQQKPGKAPKLLIYQGSLLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQSWQTPFTFGQGTKVEIKR

>DOM4-14 (SEQ ID NO:21)

DIQMTQSPSSLSASVGDRVTITCRASQEIARAALQWYQQKPGKAPKLLIYQVSILQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQSDRYPPFTFGQGTKVEIKR

>DOM4-15 (SEQ ID NO:22)

DIQMTQSPSSLSASVGDRVTITCRASQYIAEFLYWYQQKPGKAPKLLIYKASILQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYNAYPFTFGQGTKVEIKR

>DOM4-20 (SEQ ID NO:23)

DIQMTQSPSSLSASVGDRVTITCRASQSINQVLNWWYQQKPGKAPKLLIYQASLLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQFWGFPFTFGQGTKVEIKR

>DOM4-21 (SEQ ID NO:24)

DIQMTQSPSSLSASVGDRVTITCRASQSIEHWLYWYQQKPGKAPKLLIYHASQLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHLPMPFTFGQGTKVEIKR

>DOM4-22 (SEQ ID NO:25)

DIQMTQSPSSLSASVGDRVTITCRASQSIKVYLRWYQQKPGKAPKLLIYKASLLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQDFDHPSTFGQGTKVEIKR

>DOM4-23 (SEQ ID NO:26)

DIQMTQSPSSLSASVGDRVTITCRASQSIEFFLYWYQQKPGKTPKLLIYHASWLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYFSYPLTFGQGTKVEIKR

>DOM4-25 (SEQ ID NO:27)

DIQMTQSPSSLSASVEDRVTITCRASQSIYYFLHWYQQKPGKAPKLLIYRASSLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQVWRPPLTFGQGTKVEIKR

>DOM4-26 (SEQ ID NO:28)

DIQMTQSPSSLSASVGDRVTITCRASQSITVELRWYQQKPGKAPKLLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYATWPLTFGQGTKVEIKR

>DOM4-27 (SEQ ID NO:29)

DIQMTQSPSSLSASVGDRVTITCRASQSIYLSLLWYQQKPGKTPKLLIYNASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQSWEPFTFGQGTKVEIKR

FIG. 9B

8/93

>DOM4-28 (SEQ ID NO:30)
DIQMTQSPSSLSASVGDRVTITCRASQSIHLYWYQQKPGKAPKLLIYHASQLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHLPMTFGQGTKVEIKR

>DOM4-29 (SEQ ID NO:31)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYGASILQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQVWLPITFGQGTKVEIKR

>DOM4-31 (SEQ ID NO:32)
DIQMTQSPSSLSASVGDRVTITCRASQSIQQWLYWYQQKPGKAPKLLIYKASILQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYERYPFTFGQGTKVEIKR

>DOM4-32 (SEQ ID NO:33)
DIQMTQSPSSLSASVGDRVTITCRASQSIHLYWYQQKPGKAPKLLIYKASFLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQSQLLPMTFGQGTKVEIKR

>DOM4-33 (SEQ ID NO:34)
DIQMTQSPSSLSASVGDRVTITCRASQSIYNYLTWYQQKPGKAPKLLIYGASMLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQERSGPYTFGQGTKVEIKR

>DOM4-34 (SEQ ID NO:35)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYFASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQNMLLPVTFGQGTKVEIKR

>DOM4-36 (SEQ ID NO:36)
DIQMTQSPSSLSASVGDRVTITCRASQSIHLYWYQQKPGKAPKLLIYHASVLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYGDLPFTFGQGTKVEIKR

>DOM4-37 (SEQ ID NO:37)
DIQMTQSPSSLSASVGDRVTITCRASQSIGWLYWYQQKPGKAPKLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYNSTPFTFGQGTKVEIKR

>DOM4-38 (SEQ ID NO:38)
DIQMTQSPSSLSASVGDRVTITCRASQSIDRFLAWYQQKPGKAPKLLIYHASDLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQFDQWPFTFGQGTKVEIKR

>DOM4-39 (SEQ ID NO:39)
DIQMTQSPSSLSASVGDRVTITCRASQSIKSLAWYQQKPGKAPKLLIYKASLLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYSRNPITFGQGTKVEIKR

>DOM4-40 (SEQ ID NO:40)
DIQMTQSPSSLSASVGDRVTITCRASQSIKSLHWYQQKPGKAPKLLIYRASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQNRLRPHTFGQGTKVEIKR

>DOM4-41 (SEQ ID NO:41)
DIQMTQSPSSLSASVGDRVTITCRASQSIKQFLYWYQQKPGKAPKLLIYQASYLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYEVYPFTFGQGTKVEIKR

>DOM4-42 (SEQ ID NO:42)
DIQMTQSPSSLSASVGDRVTITCRASQSIYHYLYWYQQKPGKAPKLLIYAASLLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYQLYPFTFGQGTKVEIKR

>DOM4-44 (SEQ ID NO:43)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYFASLLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQGWDVPYTFGQGTKVEIKR

>DOM4-45 (SEQ ID NO:44)
DIQMTQSPSSLSASVGDRVTITCRASQSIDNWLRYWYQQKPGKAPKLLIYASFLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQGRSAPQTFGQGTKVEIKR

FIG. 9C

9/93

>DOM4-46 (SEQ ID NO:45)
 DIQMTQSPSSLSASVGDRVTITCRASQSIWYWLSWYQQKPGKAPKLLIYYASSLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQMSSTPFTFGQGTKVEIKR

>DOM4-49 (SEQ ID NO:46)
 DIQMTQSPSSLSASVGDRVTITCRASQSIWYWLSWYQQKPGKAPKLLIYNASHLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQYFDYPTFTFGQGTKVEIKR

>DOM4-50 (SEQ ID NO:47)
 DIQMTQSPSSLSASVGDRVTITCRASQSIHWLLSWYQQKPGKAPKLLIYAASSLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQNLARPTFTFGQGTKVEIKR

>DOM4-74 (SEQ ID NO:48)
 DIQMTQSPSSLSASVGDRVTITCRASQSIGERLWYQQKPGKAPKLLIYNSSVLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQSWRGPATFTFGQGTKVEIKR

>DOM4-75 (SEQ ID NO:49)
 DIQMTQSPSSLSASVGDRVTITCRASQDIDRALQWYQQKPGKAPKLLIYMSSVLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQQAGYPTFTFGQGTKVEIKR

>DOM4-76 (SEQ ID NO:50)
 DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELWYQQKPGKAPMLLIYHASRLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQYFTWPLTFTFGQGTKVEIKR

>DOM4-78 (SEQ ID NO:51)
 DIQMTQSPSSLSASVGDRVTITCRASQSISTSLQWYQQKPGKAPKLLIYSSSTLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQQWEYPTFTFGQGTKVEIKR

>DOM4-79 (SEQ ID NO:52)
 DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELWYQQKPGKAPKLLIYWASILQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQTNWPTFTFGQGTKVEIKR

>DOM4-80 (SEQ ID NO:53)
 DIQMTQSPSSLSASVGDRVTITCRASQKIDDALQWYQQKPGKAPKLLIYLASHLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQQSNWPTFTFGQGTKVEIKR

>DOM4-81 (SEQ ID NO:54)
 DIRMTQSPSSLSASVGDRVTITCRASQSISRALQWYQQKPGKAPKLLIYQSRMLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQSYLWPTFTFGQGTKVEIKR

>DOM4-82 (SEQ ID NO:55)
 DIQMTQSPSSLSASVGDRVTITCRASQEIIGKELLWYQQKPGKAPKLLIYDVSVLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQYQSYPTFTFGQGTKVEIKR

>DOM4-83 (SEQ ID NO:56)
 DIQMTQSPSSLSASVGDRVTITCRASQQIMRSLNMYQQKPGKAPKLLIYQSSILQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQAWYPTFTFGQGTKVEIKR

>DOM4-84 (SEQ ID NO:57)
 DIQMTQSPSSLSASVGDRVTITCRASQDIQRRALWYQQKPGKAPKLLIYNVSYLQSGVPS
 RFGSGSGTDFTLTISSLQPEDFATYYCQQYNDYPTFTFGQGTKVEIKR

>DOM4-85 (SEQ ID NO:58)
 EVQLLESGGGLVQPGGSLRLSCAASGFTFRMYQMYWVRQAPGKGLEWVSSISASGAGTYY
 ADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKAASSFDYWGQGLTVTVSS

>DOM4-86 (SEQ ID NO:59)
 EVQLLESGGGLVQPGGSLRLSCAASGFTFASYQMYWVRQAPGKGLEWVSTISPSGGGTYY
 ADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKKTGTDFDYWGQGLTVTVSS

>DOM4-87 (SEQ ID NO:60)

FIG. 9D

10/93

EVQLLESGGGLVQPGGSLRLSCAASGFTFNKYSMGWVRQAPGKGLEWVSRISSSGGGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKVANPFDYWGQGLTVTVSS

>DOM4-88 (SEQ ID NO:61)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNKYSMGWVRQAPGKGLEWVSRISSSGGGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKEPDRSGYLTRVAFDYWGQGLTV
TVSS

>DOM4-89 (SEQ ID NO:62)

EVQLLESGGGLVQPGGSLRLSCAASGFTFETYQMWWVRQAPGKGLEWVSISPSGSGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKMCPRCRDVVSLFDYWGQGLTV
VSS

>DOM4-90 (SEQ ID NO:63)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSEYGMWWVRQAPGKGLEWVSGITATGKMTYY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSSLPSGQGHFDYWGQGLTVTV
S

>DOM4-91 (SEQ ID NO:64)

EVQLLESGGGLVQPGGSLRLSCAASGFTFREYQMSWARQAPGKGLEWVSTISASGSGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKRFKISPVFSSFDYWGQGLTVTV
SS

>DOM4-92 (SEQ ID NO:65)

EVQLLESGGGLVQPGGSLRLSCAASGFTFAEYQMYWVRQAPGKGLEWVSISVSGAGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSRNTLTDSHRFDYWGQGLTVTV
SS

>DOM4-93 (SEQ ID NO:66)

EVQLLESGGGLVQPGGSLRLSCAASGFTFTRYQMAWVRQAPGKGLEWVSISSSGAGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKWAANFSGNYRPFKFDYWGQGLTV
TVSS

>DOM4-94 (SEQ ID NO:67)

EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYTMTWVRQAPGKGLEWVSRISSSGAGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKVGNSRVSHTFDYWGQGLTVTV
SS

>DOM4-95 (SEQ ID NO:68)

EVQLLESGGGLVQPGGSLRLSCAASGFTFAQYSMGWVRQAPGKGLEWVSRISSSGSGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKEGRPLTASLRFDYWGQGLTVTV
SS

>DOM4-96 (SEQ ID NO:69)

EVQLLESGGGLVQPGGSLRLSCAASGFTFRMYQMYWVRQAPGKGLEWVSISASGAGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKGMMPLSSFYWGQGLTVTVSS

>DOM4-97 (SEQ ID NO:70)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMSWVRQAPGKGLEWVSILDSGVFTYY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKNVSTPEGFDYWGQGLTVTVSS

>DOM4-98 (SEQ ID NO:71)

EVQLLESGGGLVQPGGSLRLSCAASGFTFETYAMSWVRQAPGKGLEWVSSIGMHGRPTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKQKTSQSGAFDYWGQGLTVTVSS

>DOM4-99 (SEQ ID NO:72)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYTMWVRQAPGKGLEWVSRISSSGAGTTY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKRTSLADVFDYWGQGLTVTVSS

>DOM4-100 (SEQ ID NO:73)

EVQLLESGGGLVQPGGSLRLSCAASGFTFRAYAMAWVRQAPGKGLEWVSTISGTGDHTYY

FIG. 9E

11/93

ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKAHGNPVS DLSFDYWGQGLVTV
SS

>DOM4-101 (SEQ ID NO:74)
EVQLLES GGG L VQ P G G S L R L S C A A S G F T F R R Y D M S W V R Q A P G K G L E W V S T I S S T G R T T Y Y
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKALETVSGAFDYWGQGLVTVSS

>DOM4-102 (SEQ ID NO:75)
DIQMTQSPSSLSASVGDRVTITCRASQNI GYSLDWYQQKPGKAPRL LIYFGSRLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQLKPPFTFGQGTKVEIKR

>DOM4-103 (SEQ ID NO:76)
DIQMTQSPSSLSASVGDRVTITCRASQRI GPSLLWYQQKPGKAPKLLIYNTSVLQSGVPS
RFRSGSGTDFTLTIS SLQPEDFATYYCQQTWNPFTFGQGTKVEIKR

>DOM4-104 (SEQ ID NO:77)
DIQMTQSPSSLSASVGDRVTITCRASQNI E SGLWYQQKPGKAPKLLIYNSSFLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQPWQSPTTFGQGTKVEIKR

>DOM4-105 (SEQ ID NO:78)
DIQMTQSPSSLSASVGDRVTITCRASQNI GQNLWYQQKPGKAPKLLIYGSSKLQSGVPP
RFGSGSGTDFTLTIS SLQPEDFATYYCQPAWQGPKTFGQGTKVEIKR

>DOM4-106 (SEQ ID NO:79)
DIQMTQSPSSLSASVGDRVTITCRASQWI SHRLMWYQQKPGKAPKLLIYRASELQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQNARMPHTFGQGTKVEIKR

>DOM4-107 (SEQ ID NO:80)
DIQMTQSPSSLSASVGDRVTITCRASQSI DTGLDWYQQKPGKAPKLLIYRVSTLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQLRRPPFTFGQGTKVEIKR

>DOM4-108 (SEQ ID NO:81)
DIQMTQSPSSLSASVGDRVTITCRASQNI GSALQWYQQKPGKAPKLLIYQISKLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQNESWPFTFGQGTKVEIKR

>DOM4-109 (SEQ ID NO:82)
DIQMTQSPSSLSASVGDRVTITCRANQRI ESSLNWYQQKPGKAPKLLIYLSSILQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQQWTPFTFGQGTKVEIKR

>DOM4-110 (SEQ ID NO:83)
DIQMTQSPSSLSASVGDRVTITCRASQNI GKSLDWYQQKPGKAPKLLIYLTSM LQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQLRPPFTFGQGTKVEIKR

>DOM4-111 (SEQ ID NO:84)
DIQMTQSPSSLSASVGDRVTITCRASQSI GKWLYWYQQKPGKAPKLLIYESSLLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQYDIYPFTFGQGTKVEIKR

>DOM4-112 (SEQ ID NO:85)
DIQMTQSPSSLSASVGDRVTITCQASQHI GEELLWYQQKPGKDPKLLIYSGSTLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQYLWVPNTFGQGTKVEIKR

>DOM4-113 (SEQ ID NO:86)
DIQMTQSPSSLSASVGDRVTITCRASQNI KTSLLWYQQKPGKAPKLLIYWASRLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQTLDWPFTFGQGTKVEIKR

>DOM4-114 (SEQ ID NO:87)
DIQMTQSPSSLSASVGDRVTITCRASQPI WYKLNWYQQKPGKAPKLLIYAASMLQSGVPS
RFGSGSGTDFTLTIS SLQPEDFATYYCQQQLIHPYTFGQGTKVEIKR

>DOM4-115 (SEQ ID NO:88)
DIQMTQSPSSLSASVGDRVTITCRASQDI DN L WYQQKPGKAPKLLIYSASLLQSGVPS

FIG. 9F

12/93

RFSGSGSGTDFTLTISLQPEDFATYYCQQAWTSPKTFGQGTKVEIKR

>DOM4-116 (SEQ ID NO:89)
DIQMTQSPSSLSASVGDRVTITCRASQSISEYLYWYQQKPGKAPKLLIYHASVLQSGVPS
RFSGSGSGTDFTLTISLQPEDSATYYCQQYAFSPRTFGQGTKVEIKR

>DOM4-117 (SEQ ID NO:90)
DIQMTQSPSSLSASVGDRVTITCRASQGIHISLQWYQQKPGKAPKLLIYQGSILQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYHFPFTFGQGTKVEIKR

>DOM4-118 (SEQ ID NO:91)
DIQMTQSPSSLSASVGDRVTITCRASQPILRALAWYQQKPGKAPKLLIYLSSHILQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQRWVQPYTFGQGTVEIKR

>DOM4-119 (SEQ ID NO:92)
DIQMTQSPSSLSASVGDRVAITCRASQRIMKALNWYQQKPGKAPKLLIYQASLLQSGVPS
RFSGGSGTDFTLTISLQPEDLATYYCQQTVDWVFTFGQGTKVEIKR

>DOM4-120 (SEQ ID NO:93)
DIQMTQSPSSLSASVGDRVTITCRASQVIDRTLYWYQQKPGKAPKLLIYNVSFLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYESKPFTFGQGTKVEIKR

>DOM4-121 (SEQ ID NO:94)
DIQMTQSPSSLSASVGDRVTITCRASQPINTFLYWYQQKPGKAPRLLIYKSSILQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYNLYPFTFGQGTKVEIKR

>DOM4-122 (SEQ ID NO:95)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYWYQQKPGKAPMLLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYANWPLTFGQGTKVEIKR

>DOM4-122-1 (SEQ ID NO:96)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRELRYWYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYHSWPLTFGQGTKVEIKR

>DOM4-122-2 (SEQ ID NO:97)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRELRYWYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYFHWPLTFGQGTKVEIKR

>DOM4-122-3 (SEQ ID NO:98)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRELRYWYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYHSWPLTFGQGTKVEIKR

>DOM4-122-4 (SEQ ID NO:99)
DIQMTQSPSSLSASVGDRVTITCRASQNIIGRELRYWYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYNSWPLTFGQGTKVEIKR

>DOM4-122-5 (SEQ ID NO:100)
DIQMTQSPSSLSASVGDRVTITCRASQIHIGVELRYWYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYGWPLTFGQGTKVEIKR

>DOM4-122-6 (SEQ ID NO:101)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRYWYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYHGWPLTFGQGTKVEIKR

>DOM4-122-7 (SEQ ID NO:102)
DIQMTQSPSSLSASVGDRVTITCRASQSIKELRYWYQQKPGKAPMLLIYHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYHSWPLTFGQGTKVEIKR

>DOM4-122-8 (SEQ ID NO:103)
DIQMTQSPSSLSASVGDRVAITCRASQIGRELRYWYQQKPGKAPMLLIHHASRLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQYNRWPLTFGQGTKVEIKR

FIG. 9G

13/93

>DOM4-122-9 (SEQ ID NO:104)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYFYWPLTFGQGTKVEIKR

>DOM4-122-10 (SEQ ID NO:105)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-11 (SEQ ID NO:106)
DIQMTQSPSSLSASVGDRVTITCRASQAIGRELRLWYQQKPGKAPMLLIHHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYNGWPLTFGQGTKVEIKR

>DOM4-122-12 (SEQ ID NO:107)
DIQMTQSPSSLSASVGDRVTITCRASQDIGRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYGFWPLTFGQGTKVEIKR

>DOM4-122-13 (SEQ ID NO:108)
DIQMTQSPSSLSASVGDRVTITCRASQDITKELRLWYQQKPGKAPMLLIHHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYHSWPLTFGQGTKVEIKR

>DOM4-122-14 (SEQ ID NO:109)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYYLWPLTFGQGTKVEIKR

>DOM4-122-15 (SEQ ID NO:110)
DIQMTQSPSSLSASVGDRVTITCRASQRIQVELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYFGWPLTFGQGTKVEIKR

>DOM4-122-16 (SEQ ID NO:111)
DIQMTQSPSSLSASVGDRVTITCRASQWIDRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-17 (SEQ ID NO:112)
DIQMTQSPSSLSASVGDRVTITCRASQSIFKELRLWYQQKPEEAPMLLIHHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-18 (SEQ ID NO:113)
DIQMTQSPSSLSASVGDRVTITCRASQEIQRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYFTWPLTFGQGTKVEIKR

>DOM4-122-19 (SEQ ID NO:114)
DIQMTQSPSSLSASVGDRVTITCRASQPIGIELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-20 (SEQ ID NO:115)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYNGWPLTFGQGTKVEIKR

>DOM4-122-21 (SEQ ID NO:116)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYYDWPLTFGQGTKVEIKR

>DOM4-122-22 (SEQ ID NO:117)
DIQMTQSPSSLSASVGDRVTITCRASQPIGRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYSGWPLTFGQGTKVEIKR

>DOM4-122-25 (SEQ ID NO:118)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPMLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

FIG. 9H

14/93

>DOM4-122-26 (SEQ ID NO:119)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKLLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-27 (SEQ ID NO:120)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPMFLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-28 (SEQ ID NO:121)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPMFLIHHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-29 (SEQ ID NO:122)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPMFLIHHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-30 (SEQ ID NO:123)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKFLIYHASRLIKGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-31 (SEQ ID NO:124)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKFLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-32 (SEQ ID NO:125)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKFLIYHASRLYKGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-33 (SEQ ID NO:126)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKFLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-34 (SEQ ID NO:127)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKLLIYHASRLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-35 (SEQ ID NO:128)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKFLIYHASRLIKGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-36 (SEQ ID NO:129)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKFLIYHASRLYKGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-37 (SEQ ID NO:130)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKLLIHHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-38 (SEQ ID NO:131)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKAPKPLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIER

>DOM4-122-39 (SEQ ID NO:132)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKDPKPLIYHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-40 (SEQ ID NO:133)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRLWYQQKPGKDPKVLIFHASRLQRGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQYHGWLPTFGQGTKVEIKR

>DOM4-122-41 (SEQ ID NO:134)

FIG. 91

15/93

DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKQLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFTYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-42 (SEQ ID NO:135)
GIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKASKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-43 (SEQ ID NO:136)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKDPKLLIHHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-44 (SEQ ID NO:137)
DIQMTQSPSSLSASVGDRVSITCRASQWIGRELRWYQQKPGKDPKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDLATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-45 (SEQ ID NO:138)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-46 (SEQ ID NO:139)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIFHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-47 (SEQ ID NO:140)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKSPKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTLGQGTKVEIKR

>DOM4-122-48 (SEQ ID NO:141)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRCQQKPGKAPKLLIFHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-49 (SEQ ID NO:142)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIHHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-50 (SEQ ID NO:143)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIHHASRLQRGVPS
RFSGSGSGADFTLTISSLQPEDFATYYCQYHGWPLTFGQWTKVEIKR

>DOM4-122-51 (SEQ ID NO:144)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLFHHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-52 (SEQ ID NO:145)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIFHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-54 (SEQ ID NO:146)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPMPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-55 (SEQ ID NO:147)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIFHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFAAYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-56 (SEQ ID NO:148)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIHHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-57 (SEQ ID NO:149)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELWDQQKPGKAPKLLIYHASRLQRGVPS

FIG. 9J

16/93

RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-58 (SEQ ID NO:150)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPTPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-59 (SEQ ID NO:151)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKQLIYHASRLQRGVPS
RFSGSGSGSDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKAEIKR

>DOM4-122-60 (SEQ ID NO:152)
DIQMTQSPSSLSASVGDRVAITCRASQWIGRELRWYQQKPGKAPKLLIFHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-61 (SEQ ID NO:153)
GIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKDPKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-62 (SEQ ID NO:154)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKVLIFHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-63 (SEQ ID NO:155)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKDPKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTSGQGTKVEIKR

>DOM4-122-64 (SEQ ID NO:156)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQEPGEAPKPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPDSDATYYCQYHGWPLTFGQGTRVEIKR

>DOM4-122-65 (SEQ ID NO:157)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQEPGKAPKLLIHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-66 (SEQ ID NO:158)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKLLIFHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDYATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-67 (SEQ ID NO:159)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPNPLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-68 (SEQ ID NO:160)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKQLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTSGQGTKVEIKR

>DOM4-122-69 (SEQ ID NO:161)
DIQMTQSPSSLSASVGDRVTITCRASQWIDRELRWYQQKPGKAPKQLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-70 (SEQ ID NO:162)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRWYQQKPGKAPKPLIYHASRLQRGVPS
RFSGSRSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-71 (SEQ ID NO:163)
DIQMTQSPSSLSASVGDRVTITCRASQWVIGRELRWYQQIPGKAPKQLIYHASRLQRGVPS
RFSGSGSGTDFTLTIGSLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

>DOM4-122-72 (SEQ ID NO:164)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELWDQKPGKAPKFLIYHASRLQRGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYHGWPLTFGQGTKVEIKR

FIG. 9K

17/93

>DOM4-122-73 (SEQ ID NO:165)
DIQMTQSPSSLSASVGDRVTITCRASQWIGRELRYQQKPGKAPKGLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHGWPFTFGQGTKVEIKR

>DOM4-123 (SEQ ID NO:166)
DIHMTQSPSSLSASVGDRVTITCRASQIHGRSLQWYQQKPGKAPKLLIYTSILQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQQGEFPFTFGQGTKVEIKR

>DOM4-124 (SEQ ID NO:167)
DIQMTQSPSSLSASVGDRVTITCRASQHIKNFLYWYQQKPGKAPKLLIYHASTLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYMDEPRTFGQGTKVEIKR

>DOM4-125 (SEQ ID NO:168)
DIQMTQSPSSLSASVGDRVTITCRASQVISVALNRYQQKPGKAPKLLIYQGSILQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQSWQWPFTFGQGTKVEIKR

>DOM4-126 (SEQ ID NO:169)
DIQMTQSPSSLSASVGDRVTITCRASQAIGNMLYWYQQKPGKAPKLLIYNASYLQSGVPS
RFSGSGSGTDFTLTISSLQPEDYATYYCQQREMIPTFGQGTKVGIKR

>DOM4-127 (SEQ ID NO:170)
DIQMTQSPSSLSASVGDRVTITCRASQDIGEELLWYQQKPGKAPKLLIYSSSLRSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYVTSPTFGQGTKVEIKR

>DOM4-128 (SEQ ID NO:171)
DIQMTQSPSSLSASVGDRVTITCRASQGIQTFLYWYQQKPGKAPKLLIYSSSILQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYGNYPFTFGQGTKVEIKR

>DOM4-129 (SEQ ID NO:172)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMLLIYHASRLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-1 (SEQ ID NO:173)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMFLIYHASRLQRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-2 (SEQ ID NO:174)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMFLIYHASRLQHGVP
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-3 (SEQ ID NO:175)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPVFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-4 (SEQ ID NO:176)
DIQLTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTIRSLQPEDFATYYCQQYHDFPLTSGQGTKVEIKR

>DOM4-129-5 (SEQ ID NO:177)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISSLQPEDYATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-6 (SEQ ID NO:178)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMFLIYHASRLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-7 (SEQ ID NO:179)
DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRYQQKPGKAPMFLIYHASRLQRGVPS
RFSGRGSGTDFSLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

FIG. 9L

18/93

>DOM4-129-8 (SEQ ID NO:180)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQRGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-9 (SEQ ID NO:181)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPRFLIYHASRLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTIGQGTKVEIKR

>DOM4-129-10 (SEQ ID NO:182)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-11 (SEQ ID NO:183)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQRGVPS
RFGSGSGTYFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-12 (SEQ ID NO:184)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-13 (SEQ ID NO:185)
DIQMTQSPSSLSASVGDRVTITCRASQSIQRELRLWYQQKPGKAPMFLIYHASRLQRGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-14 (SEQ ID NO:186)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-15 (SEQ ID NO:187)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-16 (SEQ ID NO:188)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQRGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVENKR

>DOM4-129-17 (SEQ ID NO:189)
EIKMTQSPSSLSASVGDRVTITCRASKNIQRELRLWYQQKPGKAPMFLIYHASRLQKGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-18 (SEQ ID NO:190)
PIVMTQSPSSLSASVGDRVTITCRASSIQRELRLWYQQKPGKAPMFLIYHASRLMKGVP
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-19 (SEQ ID NO:191)
DIQMTQSPSSLSASVGDRVTITCRASNIQRELRLWYQQKPGKAPMFLIYHASRLMKGVP
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-20 (SEQ ID NO:192)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQKGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-21 (SEQ ID NO:193)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQKGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-22 (SEQ ID NO:194)
DIQMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPMFLIYHASRLQKGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQYHDFPLTIGQGTKVEIKR

>DOM4-129-23 (SEQ ID NO:195)

FIG. 9M

19/93

DIQMTQSPSSLSASVGDRVTITCRASQNIIDRELRLWYQQKPGKAPMFLIYHASRLQKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-24 (SEQ ID NO:196)
NIDMTQSPSSLSASVGDRVTITCRASQNIIDRELRLWYQQKPGKAPMFLIYHASRLYKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-25 (SEQ ID NO:197)
HISMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLIKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-26 (SEQ ID NO:198)
EIRMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLYKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-27 (SEQ ID NO:199)
RIVMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLIKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-28 (SEQ ID NO:200)
PIRMTQSPSSLSASVGDRVTITCRASANIDRELRLWYQQKPGKAPMFLIYHASRLIKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-29 (SEQ ID NO:201)
TISMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLYRGAPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-31 (SEQ ID NO:202)
RILMTQSPSSLSASVGDRVTITCRASLNIDRELRLWYQQKPGKAPMFLIYHASRLHKGVP
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-32 (SEQ ID NO:203)
GIVMTQSPSSLSASVGDRVTITCRASINIDRELRLWYQQKPGKAPMFLIYHASRLHKGAPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-33 (SEQ ID NO:204)
SIVMTQSPSSLSASVGDRVTITCRASQNIIDRELRLWYQQKPGKAPMFLIYHASRLHKGVP
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-34 (SEQ ID NO:205)
DILMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLYKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTLGQGTKVEIKR

>DOM4-129-35 (SEQ ID NO:206)
QINMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLIKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-37 (SEQ ID NO:207)
TIQMTQSPSSLSASVGDRVTITCRASENIDRELRLWYQQKPGKAPMFLIYHASRLIKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-38 (SEQ ID NO:208)
QILMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLMKGVP
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-39 (SEQ ID NO:209)
QIVMTQSPSSLSASVGDRVTITCRASQNIIDRELRLWYQQKPGKAPMFLIYHASRLYKGVPS
RFGSGSGGTDFTLTISSLQPEDFATYYCQYHDFPLTFGQGTKVEIKR

>DOM4-129-40 (SEQ ID NO:210)
DILMTQSPSSLSASVGDRVTITCRASNIDRELRLWYQQKPGKAPMFLIYHASRLMKGVP

FIG. 9N

20/93

RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-41 (SEQ ID NO:211)

GIEMTQSPSSLSASVGDRVTITCRASNNIDRELRWYQQKPGKAPMFLIYHASRLHRGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-42 (SEQ ID NO:212)

GIVMTQSPSSLSASVGDRVTITCRASNNIDRELRWYQQKPGKAPMFLIYHASRLYKGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-43 (SEQ ID NO:213)

PIKMTQSPSSLSASVGDRVTITCRASNNIDRELRWYQQKPGKAPMFLIYHASRLMHGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-129-44 (SEQ ID NO:214)

NIVMTQSPSSLSASVGDRVTITCRASQNNIDRELRWYQQKPGKAPMFLIYHASRLYKGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYHDFPLTFGQGTKVEIKR

>DOM4-130 (SEQ ID NO:215)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-1 (SEQ ID NO:216)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-2 (SEQ ID NO:217)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFFFPYTFGQGTKVEIRR

>DOM4-130-3 (SEQ ID NO:218)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-4 (SEQ ID NO:219)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFFHPYTFGQGTKVEIRR

>DOM4-130-5 (SEQ ID NO:220)

DIQMTQSPSSLSASVGDRVTITCRASQDIFLNLEWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-6 (SEQ ID NO:221)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFLFPYTFGQGTKVEIRR

>DOM4-130-7 (SEQ ID NO:222)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-8 (SEQ ID NO:223)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-9 (SEQ ID NO:224)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPRLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-10 (SEQ ID NO:225)

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQPSFYLPYTFGQGTKVEIRR

FIG. 90

21/93

>DOM4-130-11 (SEQ ID NO:226)
DIQVTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-12 (SEQ ID NO:227)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFWMPYTFGQGTKVEIRR

>DOM4-130-13 (SEQ ID NO:228)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYHPYTFGQGTKVEIRR

>DOM4-130-14 (SEQ ID NO:229)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-15 (SEQ ID NO:230)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-16 (SEQ ID NO:231)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-17 (SEQ ID NO:232)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-18 (SEQ ID NO:233)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-19 (SEQ ID NO:234)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-20 (SEQ ID NO:235)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFMFPYTFGQGTKVEIRR

>DOM4-130-21 (SEQ ID NO:236)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVENRR

>DOM4-130-22 (SEQ ID NO:237)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFVFPYTFGQGTKVEIRR

>DOM4-130-23 (SEQ ID NO:238)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLFPYTFGQGTKVEIRR

>DOM4-130-24 (SEQ ID NO:239)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-25 (SEQ ID NO:240)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSNLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

FIG. 9P

22/93

>DOM4-130-26 (SEQ ID NO:241)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-27 (SEQ ID NO:242)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIHGTSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-28 (SEQ ID NO:243)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSLQSGVPS
RFGSGSGADFTLTISSLQPEDFATYYCQPSFLYPYTFGQGTKVEIRR

>DOM4-130-31 (SEQ ID NO:244)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGSYSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-32 (SEQ ID NO:245)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIRGVSELQSGVPS
RFGSGSGTEFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-33 (SEQ ID NO:246)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISLASELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-34 (SEQ ID NO:247)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIGLTSDLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-35 (SEQ ID NO:248)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSLQSGVPS
RFGSGSGYGTFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKLEIRR

>DOM4-130-36 (SEQ ID NO:249)
DIQMTQAPSSLSASVGDRVTITCRASQDIYLNLDWYQQTPGNAPKLLIYGTSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-37 (SEQ ID NO:250)
DIQMTQSPSSLSASVGDRVTITCRASQVIYLNLDWYQQKPGKAPRLLIYGTSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-38 (SEQ ID NO:251)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIRTSSDLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-39 (SEQ ID NO:252)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLITVGSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-40 (SEQ ID NO:253)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIALVSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-41 (SEQ ID NO:254)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIHHCSELQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-42 (SEQ ID NO:255)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKASKLLISSSDLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIRR

>DOM4-130-43 (SEQ ID NO:256)

FIG. 9Q

23/93

DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLISLVSDLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-44 (SEQ ID NO:257)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLISLSSDLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYAFGQGTKVEIRR

>DOM4-130-45 (SEQ ID NO:258)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLILYSSSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-46 (SEQ ID NO:259)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-47 (SEQ ID NO:260)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLISWSSFLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-48 (SEQ ID NO:261)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSDLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-49 (SEQ ID NO:262)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYGTSDLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-50 (SEQ ID NO:263)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-51 (SEQ ID NO:264)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-52 (SEQ ID NO:265)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLIYFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIRR

>DOM4-130-53 (SEQ ID NO:266)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIKR

>DOM4-130-54 (SEQ ID NO:267)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIKR

>DOM4-130-55 (SEQ ID NO:268)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIKR

>DOM4-130-56 (SEQ ID NO:269)
DIQMTQSPSSLSASVGDRVITITCRASQRIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIKR

>DOM4-130-57 (SEQ ID NO:270)
DIQMTQSPSSLSASVGDRVITITCRASQAIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQPSFYFPPYTFGQGTKVEIKR

>DOM4-130-58 (SEQ ID NO:271)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS

FIG. 9R

24/93

RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-59 (SEQ ID NO:272)
DIQMTQSPSSLSASVGDRVTITCRASQTIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-60 (SEQ ID NO:273)
DIQMTQSPSSLSASVGDRVTITCRASQSIYLNLDWYQQKPGKAPTLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-61 (SEQ ID NO:274)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPAFYFPYTFGQGTKVEIKR

>DOM4-130-62 (SEQ ID NO:275)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPGFYFPYTFGQGTKVEIKR

>DOM4-130-63 (SEQ ID NO:276)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSYFPYTFGQGTKVEIKR

>DOM4-130-64 (SEQ ID NO:277)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSGYFPYTFGQGTKVEIKR

>DOM4-130-65 (SEQ ID NO:278)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFAFPYTFGQGTKVEIKR

>DOM4-130-66 (SEQ ID NO:279)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFLFPYTFGQGTKVEIKR

>DOM4-130-67 (SEQ ID NO:280)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYHPYTFGQGTKVEIKR

>DOM4-130-68 (SEQ ID NO:281)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYWPYTFGQGTKVEIKR

>DOM4-130-69 (SEQ ID NO:282)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPPTFGQGTKVEIKR

>DOM4-130-70 (SEQ ID NO:283)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGWGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-71 (SEQ ID NO:284)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-72 (SEQ ID NO:285)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLMWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-73 (SEQ ID NO:286)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLLWYQQKPGKAPRLLINFGSELQSGVPS
RFSGSGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

FIG. 9S

25/93

>DOM4-130-74 (SEQ ID NO:287)
DIQMTQSPSSLSASAGDRVITITCRASQDIYLNLMWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-75 (SEQ ID NO:288)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLAWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-76 (SEQ ID NO:289)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLLWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-77 (SEQ ID NO:290)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLTWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-78 (SEQ ID NO:291)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLPWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-79 (SEQ ID NO:292)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNWKYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-80 (SEQ ID NO:293)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLTWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-81 (SEQ ID NO:294)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLEWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-82 (SEQ ID NO:295)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELTSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-83 (SEQ ID NO:296)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELNSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-84 (SEQ ID NO:297)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELYSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-85 (SEQ ID NO:298)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELFSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-86 (SEQ ID NO:299)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELLSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-87 (SEQ ID NO:300)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELRSVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-88 (SEQ ID NO:301)
DIQMTQSPSSLSASVGDRVITITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELPSGVPS
RFGSGYGTDFLTITISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

FIG. 9T

26/93

>DOM4-130-89 (SEQ ID NO:302)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKPLINFGSELQPGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-90 (SEQ ID NO:303)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQPGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-91 (SEQ ID NO:304)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQHGVP
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-92 (SEQ ID NO:305)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQLGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-93 (SEQ ID NO:306)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQKGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-94 (SEQ ID NO:307)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQFGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-95 (SEQ ID NO:308)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQQGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-96 (SEQ ID NO:309)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCTPSFYFPYTFGQGTKVEIKR

>DOM4-130-97 (SEQ ID NO:310)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCKPSFYFPYTFGQGTKVEIKR

>DOM4-130-98 (SEQ ID NO:311)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFAMYYCAPSFYFPYTFGQGTKVEIKR

>DOM4-130-99 (SEQ ID NO:312)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCSPSFYFPYTFGQGTKVEIKR

>DOM4-130-100 (SEQ ID NO:313)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCLPSFYFPYTFGQGTKVEIKR

>DOM4-130-101 (SEQ ID NO:314)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQASFYFPYTFGQGTKVEIKR

>DOM4-130-102 (SEQ ID NO:315)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISGLQPEDFATYYCQASFYFPYTFGQGTKVEIKR

>DOM4-130-103 (SEQ ID NO:316)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQGSFYFPYTFGQGTKVEIKR

>DOM4-130-104 (SEQ ID NO:317)

FIG. 9U

27/93

DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-105 (SEQ ID NO:318)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLITFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-106 (SEQ ID NO:319)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIMFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-107 (SEQ ID NO:320)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIVFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-108 (SEQ ID NO:321)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLIKFGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-109 (SEQ ID NO:322)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELQSGVPS
RFRSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-110 (SEQ ID NO:323)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINYGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-111 (SEQ ID NO:324)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINSGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-112 (SEQ ID NO:325)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINLGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-113 (SEQ ID NO:326)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINGGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-114 (SEQ ID NO:327)
DIQMTQSPSSLSASVGDRVTITCRASQDIYPNLDWYQQKPGKAPKLLINSGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-115 (SEQ ID NO:328)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINLGSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-116 (SEQ ID NO:329)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFSSSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-117 (SEQ ID NO:330)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFASELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-118 (SEQ ID NO:331)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFVSELQSGVPS
RFGSGGYGTDFTLTISLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-119 (SEQ ID NO:332)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSSLQSGVPS

FIG. 9V

28/93

RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-120 (SEQ ID NO:333)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSALQSGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-121 (SEQ ID NO:334)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSTLQSGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-122 (SEQ ID NO:335)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSDLQSGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-123 (SEQ ID NO:336)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELRSQGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-124 (SEQ ID NO:337)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELQPGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-125 (SEQ ID NO:338)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELRPGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-126 (SEQ ID NO:339)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELRPGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-127 (SEQ ID NO:340)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELQKGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-128 (SEQ ID NO:341)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELRKGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-129 (SEQ ID NO:342)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLINFGSELRKGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-130 (SEQ ID NO:343)
DIQMTQSPSSLSASVGDRVTITCRASQTIYLNLDWYQQKPGKAPKLLISFGSELQKGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQPSFYFPYTFGQGTKVEIKR

>DOM4-130-131 (SEQ ID NO:344)
DIQMTQSPSSLSASVGDRVTITCRASQTIYLNLDWYQQKPGKAPKLLINFGSELQSGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQAFYFPYTFGQGTKVEIKR

>DOM4-130-132 (SEQ ID NO:345)
DIQMTQSPSSLSASVGDRVTITCRASQDIYLNLDWYQQKPGKAPKLLISFGSELQKGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQAFYFPYTFGQGTKVEIKR

>DOM4-130-133 (SEQ ID NO:346)
DIQMTQSPSSLSASVGDRVTITCRASQTIYLNLDWYQQKPGKAPKLLISFGSELQKGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQAFYFPYTFGQGTKVEIKR

>DOM4-131 (SEQ ID NO:347)
DIQMTQSPSSLSASVGDRVTITCRASQIYNALRWYQQKPGKARKLLIYHKSQSGVPS
RFSGSGYGTDFTLTISSLQPEDFATYYCQQTYSFPHTFGQGTKVEIKR

FIG. 9W

29/93

>DOM4-132 (SEQ ID NO:348)
DIQMTQSPSSLSASVGDRVTITCRASQDIWLNLSWYQQKPGKAPKLLIYDGSTLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQPSFIWPTYFGQGTKVEIKR

>DOM4-133 (SEQ ID NO:349)
DIKMTQSPSSLSASVGDRVTITCRASQNIQRELRLWYQQKPGKAPKLLIYHASHLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQYYFYFPLTFGQGTKVEIKR

FIG. 9X

30/93

CDRs are underlined: CDR1, CDR2 and CDR3.

>DOM4-122-23 (SEQ ID NO:350)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-24 (SEQ ID NO:351)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-30 (SEQ ID NO:352)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCGATTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-46 (SEQ ID NO:353)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-51 (SEQ ID NO:354)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-53 (SEQ ID NO:355)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-54 (SEQ ID NO:356)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10A

31/93

>DOM4-1 (SEQ ID NO:357)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATTTATTTTACATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCGGGCATCCTCTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGTGTGGCGTCTCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-2 (SEQ ID NO:358)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATCAGAGTTTAGATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTATGCATCCGTGTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCTGTCTCGTCCGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-3 (SEQ ID NO:359)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTACATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGTGCAAGTCAGAGCATTGAGGAGATGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATGCATCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGTGGTGGGTACGCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-4 (SEQ ID NO:360)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGATGATTATTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTGGGCATCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAGGTGGTTGACGCCTTCGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-5 (SEQ ID NO:361)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGAGGAGATGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATGCATCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGTGGTGGGTACGCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-6 (SEQ ID NO:362)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGATGATTATTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTGGGCATCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGTAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAAGTGGATGGGTCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-7 (SEQ ID NO:363)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAACATTGATTGGGGTTAGATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATATGGCATCCCGTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTTGAGTATGTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10B

32/93

>DOM4-8 (SEQ ID NO:364)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTCTGGATTATTTAAGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTGGGCATCCAAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAAGTGGATGGGTCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-9 (SEQ ID NO:365)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTCTGAGTATTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCATCCACTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTGACAGTATCTGCGCCTCCTTTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-10 (SEQ ID NO:366)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCCGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGGGTGAGTTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGAGTTCCTGTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTGTATATTTTCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-11 (SEQ ID NO:367)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCCTATTGAGCGTTGGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTGGTCCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGAGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGCGTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-12 (SEQ ID NO:368)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGAGTGGTATTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTTCGTCCTTGTGCAAAGTGGGGTCCCATCA
CGTTTTAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGATTGGTCTTCTCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-13 (SEQ ID NO:369)
GACATCCAGATGACCCAGTCTCCATCCTTTCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGTTATTGGGATTACGTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGGGATCCTTGTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAACAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTCTGTCGTCAGACGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-14 (SEQ ID NO:370)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGAGATTCTGTGCTGCGTTACAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGGTTTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTCTGATAGGTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10C

33/93

>DOM4-15 (SEQ ID NO:371)
GACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTATATTGCGGAGTTTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATAAGGCTTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATAATGCTTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-16 (SEQ ID NO:372)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTCACCTTTCTGAGTATCGGATGGCTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTGGAGTGGGTCTCATCTATTGAGGGTGATGGTCATATTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTATATTACTGTGCGAAATCGGAT
ATTTCTGATGATCAGTTTGACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-17 (SEQ ID NO:373)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGAGATGTATAAGATGGCGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACTATTTGAGTCTGTTGGTACGACTTACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATTTCTG
GGTAGTGGGAGTCGTTTGACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-18 (SEQ ID NO:374)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGCGCGTTATACGATGAATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTGGTGCAGGGTCAGGATACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTATATTACTGTGCGAAATATAAT
AGTAAGCATGCGTTTGACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-19 (SEQ ID NO:375)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTCTGTCGTATCAGATGGCTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTAGTGGGAATGGTAGTCGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTATATTACTGTGCGAAAAGTGGG
CCGAATGGGGGGATGTTTGACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-20 (SEQ ID NO:376)
GACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAATCAGGTGTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATCATGCATCCAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTTTTGGGGTTTTCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-21 (SEQ ID NO:377)
GACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGAGCATTGGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATCATGCATCCAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATCATTTGCCGCCTATGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10D

34/93

>DOM4-22 (SEQ ID NO:378)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAAAGGTTTATTTACGGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAAGGCATCCCTTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGATTTTGATCATCCTTCGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-23 (SEQ ID NO:379)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGAGTTTATTTTATATTGGTACCAGCAGAAACCA
GGGAAAACCCCTAAGCTCCTGATCTATCATGCATCCTGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTTTAGTTATCCTTTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-25 (SEQ ID NO:380)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATTTATTTTACATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCGGGCATCCTCTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGTGTGGCGTCTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-26 (SEQ ID NO:381)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTACTGTTGAGTTAAGGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCATCCCGTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGCTACTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-27 (SEQ ID NO:382)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATCTGAGTTTATTGTGGTACCAGCAGAAACCA
GGGAAAACCCCTAAGCTCCTGATCTATAATGCATCCCGTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTCGTGGGAGTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-28 (SEQ ID NO:383)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGAGCATTGGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCATCCAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATTGCGCCTATGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-29 (SEQ ID NO:384)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTGCATCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTGGGTTGGTTGCCTATTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10E

35/93

>DOM4-31 (SEQ ID NO:385)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGTGGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAAGGCATCCATTTTGCAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGAGCGGTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-32 (SEQ ID NO:386)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTACTCATGCGTTAAAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAAGGCATCCTTTTGCAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTCTCAGCTTCTTCTATGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-33 (SEQ ID NO:387)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATAATTATTTAACTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTGCATCCATGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGAGAGGTCTGGTCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-34 (SEQ ID NO:388)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGTATTTTAAATGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTTTGCATCCCGTTTGCAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAATATGCTGTTGCCTGTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-36 (SEQ ID NO:389)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGGCATTTTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCATCCGTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGGGGATTTGCCTTTTACGTTTCGGTCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-37 (SEQ ID NO:390)

GACATCCAGATGACCCAGTCTCCACCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGGGTGGTGGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCATCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATAATTCTACGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-38 (SEQ ID NO:391)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGATAGGTTTTTAGCTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCATCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTTTGATCAGTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10F

36/93

>DOM4-39 (SEQ ID NO:392)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAAAGAGTAGGTTAGCGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAAGGCATCCCTTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATAGTAGGAATCCTATTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-40 (SEQ ID NO:393)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGTCGGTCTTTACATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCGGGCATCCCGTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAAATCGGCTTAGGCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-41 (SEQ ID NO:394)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAAAGCAGTTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGGCATCCTATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGAGGTTTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-42 (SEQ ID NO:395)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATCATATTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCCTTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCAGCTTTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-44 (SEQ ID NO:396)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTTTGTCATCCTCTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGGTTGGGATGTGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-45 (SEQ ID NO:397)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGATAATTGGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAGTGCATCCTTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGGGCGTTTCGGCGCCTCAGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-46 (SEQ ID NO:398)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTGGTATTGGTTAAGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTATGCATCCAGTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAAGCAGATGTCGAGTACTCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10G

37/93

>DOM4-49 (SEQ ID NO:399)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTACGATGAGGTTAGGGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATGCATCCCATTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTTTGATTATCCTACGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-50 (SEQ ID NO:400)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGCATTATGGCTGTATCGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGTGCATCCAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAATTTGGCTAGGCCTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-51 (SEQ ID NO:401)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGTT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTTCTTTTCATGGTACGCCTACAGGGTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCGAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGGGATG
TTTTATTTTGACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-52 (SEQ ID NO:402)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAATGGGTATGATATGTTTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTTCCGATTCCGGGTCTGTGACACGGTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCGAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATCTTGG
GATGAGTTTGACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-53 (SEQ ID NO:403)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGGTTTCGTATAAGATGGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTACTAAGGATGGTTCTAAGACAGCTTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCGAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATTTCCG
CCGAAGTTTGAATACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-54 (SEQ ID NO:404)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCGAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGGGCGT
TTTAGTTTGAATACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-55 (SEQ ID NO:405)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGGAATTATGATATGAATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCGAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGGGTTG
CATACGTTTGACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

FIG. 10H

38/93

>DOM4-56 (SEQ ID NO:406)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGGGTTGTATTGGATGAGTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTGATCAGCTGGGTGTTTCTACATTTTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGGGTAT
GTTTATTTTACTACTGAGGCGCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-57 (SEQ ID NO:407)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTCTCTGTATGCGATGACTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGGGTGC
AGGTATTTTACTACTGAGGCGCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-58 (SEQ ID NO:408)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTTATAAGTATTTGATGTGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGAGGGT
TTGGGGTTTACTACTGAGGCGCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-59 (SEQ ID NO:409)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTTCGTAAGTATAAGATGGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATATCAT
TTGCAGTGGGGTCATAATTTTACTACTGAGGCGCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-60 (SEQ ID NO:410)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATATCAG
ACGCGGGTGGGTGATGGTTTACTACTGAGGCGCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-61 (SEQ ID NO:411)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGCGATG
TCTATGGCGGGTTCGGCTTTTACTACTGAGGCGCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-62 (SEQ ID NO:412)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGACACAGCCT
AGGGCGCTGGCTGGTTATTTTACTACTGAGGCGCAGGGACCTGGTCACCGTCTCGAGC

FIG. 10I

39/93

>DOM4-63 (SEQ ID NO:413)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAACGCTT
TCGGGTTCTGATATGGCGTTTACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-64 (SEQ ID NO:414)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGGTATG
ACTGTTGGGCATTTTCAGTTTACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-65 (SEQ ID NO:415)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGCGTTT
GCGCATGTGATGGGGGTTTTACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-66 (SEQ ID NO:416)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGCTATG
AGTCATAAGTTTCAGGGGTTTACTACTGGGGCCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-67 (SEQ ID NO:417)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGGTGGTTATGCTATGGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGGATTTGCGCGTCCGGTGGGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAATGATT
CAGGGGCTTAGGTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-68 (SEQ ID NO:418)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGCGGCTTATTGATGTGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGTATTGCTCCTGATGGTACTCATACTACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAATGGCTT
GAGCTTCCTATTTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-69 (SEQ ID NO:419)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTCTTATTATCATATGGCGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTACGCCCTTCGGGTGGTCAGACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAATTCAT
CGTGCGGGGCTGCTAGTAATTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTCG
AGC

FIG. 10J

40/93

>DOM4-70 (SEQ ID NO:420)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGGTGCATGATGAGATGAATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTGATAGTAAGGGTTTAAAGACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATCTTCG
GTGACGTCTCTTTGGCGTATAGTAGGCATTTTGAATACTGGGGTCAGGGAACCTGGTC
ACCGTCTCGAGC

>DOM4-71 (SEQ ID NO:421)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTTCGAATTATGATATGGCTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGTATTTTCGGATATGGGTAGGGCTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAATTTTT
GCTACTAATGGGATGCTTTCTGGGGCTTTTGAATACTGGGGTCAGGGAACCTGGTCACC
GTCTCGAGC

>DOM4-72 (SEQ ID NO:422)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTTCGGGATTATCCGATGAGTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTTATTCTTGGGGTTCTAAGACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTATATTACTGTGCGAAAATGGCG
CAGGCGGAGACTTCGCCTAATAATTATTTTGAATACTGGGGTCAGGGAACCTGGTCACC
GTCTCGAGC

>DOM4-73 (SEQ ID NO:423)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGATGATTATAAGATGAGTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTAATGGTTCTGGGCAGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAATCTCTG
GCTTTGGCGTCTACTCGGCATACTGGTTTTTGAATACTGGGGTCAGGGAACCTGGTCACC
GTCTCGAGC

>DOM4-74 (SEQ ID NO:424)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGTCTATTGGGGAGAGGTTATGGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATAGTTCCGTGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCAACATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAGTTGGAGGGGGCTGTACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-75 (SEQ ID NO:425)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGGATATTGATCGGGCTTTACAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATATGAGTTCCGTTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCAACATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGGCTGGGTATCCTTTTACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-76 (SEQ ID NO:426)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGAAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTTTACTTGGCCTTTACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

FIG. 10K

41/93

>DOM4-78 (SEQ ID NO:427)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGTATTAGTACTTCGTTACAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTCTAGTTCCACGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGTGGGAGTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-79 (SEQ ID NO:428)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAAATATTGGTACGGCGTTATCTTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTGGGCTTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGACTAATTCTTGGCCTTTTACGTTTGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-80 (SEQ ID NO:429)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAAGATTGATGATGCGTTACAGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTGGCGTCCCATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTTTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGAGTAATTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-81 (SEQ ID NO:430)

GACATCCGGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGTATTGGGCGGGCGTTACAGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGCGTTCCATGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAGTTATCTGTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-82 (SEQ ID NO:431)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGAGATTGGGAAGGAGTTATTGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGATGTTTCCGTTTTCGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCAGTCTTATCCTAATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-83 (SEQ ID NO:432)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCAGATTATGAGGAGTTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGAGTTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGCGTGGCAGTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-84 (SEQ ID NO:433)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTCAGCGGCGTTAGCTTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATGTGTCTTATTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATAATGATTATCCTACGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10L

42/93

>DOM4-85 (SEQ ID NO:434)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGGATGTATCAGATGTATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGTATTAGTGGTCTGGTGCAGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGCTGCT
AGTAGTTTTGACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-86 (SEQ ID NO:435)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGTATCAGATGTATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACTATTAGTCTTCTGGTGGGGGGACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGGAT
ACTGGTACGTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-87 (SEQ ID NO:436)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGTTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAATAAGTATTCTATGGGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGTATTTCTTCTTGGGTGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGTTGCT
AATCCGTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTCGAGC

>DOM4-88 (SEQ ID NO:437)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAATAAGTATTCTATGGGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGTATTTCTTCTTGGGTGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGAGCCT
GATAGGTCTGGGTATCTTACTAGGGTGGCGTTTACTACTGGGGTCAGGGAACCTGGTC
ACCGTCTCGAGC

>DOM4-89 (SEQ ID NO:438)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGAGACTTATCAGATGTGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGTATTTCTCCGAGTGGTTCTGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTTTATTACTGTGCGAAAATGTGT
CCTCGTTGTAGGGATGTGGTTAGTCTTTTACTACTGGGGTCAGGGAACCTGGTCACC
GTCTCGAGC

>DOM4-90 (SEQ ID NO:439)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTTCGGAGTATGGTATGTGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAGGTATTACTGCTACTGGTAAGATGACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAATCGAGT
CTTCCTTCGGGTACGGTCAATTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTCG
AGC

>DOM4-91 (SEQ ID NO:440)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTTCGTGAGTATCAGATGTCTGGGCCCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTAGTGCTTCGGGTAGTGGGACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTATATTACTGTGCGAAAACGGTTT
AAGATTTCTCCGGTTTGTAGTAGTTTACTACTGGGGTCAGGGAACCTGGTCACCGTCTC
TCGAGC

FIG. 10M

43/93

>DOM4-92 (SEQ ID NO:441)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGCGGAGTATCAGATGTATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTTCTGTGTCTGGTGCTGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATCGCGG
AATACGCTGACGGATTTCGCATCGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGTC
TCGAGC

>DOM4-93 (SEQ ID NO:442)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTACGAGGTATCAGATGGCGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTTGAGTAGTGGTGCGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATGGGCG
GCTAATTTTTCGGGTAATTATAGGCCTAAGTTTGGACTACTGGGGTCAGGGAACCCCTGGTC
ACCGTCTCGAGC

>DOM4-94 (SEQ ID NO:443)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAAGGATTATACGATGACGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTGGAGTGGGTCTCAAGGATTTGTCGTCGTCGGGTGCGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTATATTACTGTGCGAAAGTTGGG
AATTCTAGTAGGGTGTCTCATACTTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGTC
TCGAGC

>DOM4-95 (SEQ ID NO:444)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGCGCAGTATTCTATGGGGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTGGAGTGGGTCTCAAGGATTTGAGTTCCGGTAGTGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGAGGGT
AGGCCCTCTTACGGCTTCTTTGCGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGTC
TCGAGC

>DOM4-96 (SEQ ID NO:445)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACGGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGGATGTATCAGATGTATTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGTATTAGTGCCTCTGGTGCGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAGGTATG
ATGCCGCTGAGTTCTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

>DOM4-97 (SEQ ID NO:446)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGGGAAGTATTCTATGTGCTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGTATTCTGGATTCCGGTGTTTTTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTAC
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAATGTT
TCGACTCCGGAGGGGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

FIG. 10N

44/93

>DOM4-98 (SEQ ID NO:447)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTGAGACTTATGCGATGAGTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTGGTATGCATGGTAGGCCTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAACAGAAG
ACTTCTCAGTCGGGGGCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM4-99 (SEQ ID NO:448)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTAGTTCGTATACGATGGAGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAAGGATTTCTGTCGTGGGTGCGGGTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGGACT
TCTTTGGCTGATGTGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM4-100 (SEQ ID NO:449)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTCTGTCGTATGCGATGGCTTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTTCTGGTACTGGTGATCATACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGCTCAT
GGTAATCCGGTTTCGGATCTTTCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTC
TCGAGC

>DOM4-101 (SEQ ID NO:450)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTC
TCCTGTGCAGCCTCCGGATTACCTTTCTGTCAGGTATGATATGTCGTGGGTCCGCCAGGCT
CCAGGGAAGGGTCTAGAGTGGGTCTCAACGATTTCTAGTACGGGTCCGACTACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAAAGCGCTT
GAGACTGTTTCTGGGGCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM4-102 (SEQ ID NO:451)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCTAGTCAGAATATTGGTTATAGTTTAGATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAGGCTCCTGATCTATTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCTGCTGAAGCCGCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-103 (SEQ ID NO:452)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGAGGATTGGGCCTAGTTTATTTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATACTTCCGTGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGGGGCAAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGACTTGAATATATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-104 (SEQ ID NO:453)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGAATATTGAGTCTGGTTTATGGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATTCGTCCTTTTGGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCCGTGGCAGAGTCTTACGAGTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

FIG. 100

45/93

>DOM4-105 (SEQ ID NO:454)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGGTCAGAATTTATGGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAGGGTCGTCCAAGTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGGCTTGGCAGGGGCCTAAGACGTTTCGGCCAA
GGGACCAAGGTGGAGATCAAACGG

>DOM4-106 (SEQ ID NO:455)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTTTCGCATCGTTTAAATGGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAGGGTCGTCCAAGTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAATGCGAGGATGCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-107 (SEQ ID NO:456)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGATATTGATACTGGTTTAGATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAGGGTCCTCACGTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCTTCGTCTCCGCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-108 (SEQ ID NO:457)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGGGTCTGCGTTACAATGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGATTTCCAAGTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAATGAGAGTTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-109 (SEQ ID NO:458)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGATTGAGAGTTCTTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTTGTCGTCCATTTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGTGGACTTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-110 (SEQ ID NO:459)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGGTAAGTCTTTAGATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTTGACTTCCATGTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTTCAGCGTCCTCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-111 (SEQ ID NO:460)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCTATTGGTAAGTGGTTATATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGAGTCGTCCCTGTTGCAAAGTGGGGTCCCACCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGACATTTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10P

46/93

>DOM4-112 (SEQ ID NO:461)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCAGGCAAGTCAGCATATTGGTGAGGAGTTACTTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATTCTGGTTCCACGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCTTGTGTGGCCTAATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-113 (SEQ ID NO:462)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTAAGACTTCGTTATTGTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATTGGGCTTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGACTTTGGATTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-114 (SEQ ID NO:463)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCCGATTTGGTATAAGTTAAATTGGTATCAGCAAAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGCGGCTTCCATGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGCTTATTCATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-115 (SEQ ID NO:464)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTGATAATAATTTATGGTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATTGCGCTTCCTTGTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGGCTTGGACGAGTCCTAAGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-116 (SEQ ID NO:465)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCTATTAGTGAGTATTTATATTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATCATGCGTCCGTTTTCGCAACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTCTGCTACGTACTACTGTCAACAGTATGCGTTTTCTCCTAGGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-117 (SEQ ID NO:466)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGGGATTCATATTAGTTTACAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATCAGGGGTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTTACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGTATCATTTTCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-118 (SEQ ID NO:467)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCCTATTTTGGCTGCGTTAGCGTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATTGTGCTGCCATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAGGTGGGTGCAGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10Q

47/93

>DOM4-119 (SEQ ID NO:468)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCGC
ATCACTTGCCGGGCAAGTCAGAGGATTATGAAGGCGTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGGCGTCCCTTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCGGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGGCTACGTACTACTGTCAACAGACGGATGTTTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-120 (SEQ ID NO:469)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGGTGATTGATCGGACTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATGTTTCTTTCTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGAGTCGAAGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-121 (SEQ ID NO:470)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGCCGATTAATACTTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAGGCTCCTGATCTATAAGTCGTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATAATCTGTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122 (SEQ ID NO:471)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGCTAATTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-1 (SEQ ID NO:472)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGTCGATTGGTCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATAGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-2 (SEQ ID NO:473)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGTCTATTGGGCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTTTCATTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-3 (SEQ ID NO:474)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAAC
ATCACTTGCCGGGCAAGTCAGTCGATTGGTCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATAGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10R

48/93

>DOM4-122-4 (SEQ ID NO:475)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGGTCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATAATTTCGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-5 (SEQ ID NO:476)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCATATTGGGGTTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-6 (SEQ ID NO:477)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-7 (SEQ ID NO:478)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCTATTACTAAGGAGCTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATTCTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-8 (SEQ ID NO:479)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTGCGC
ATCACTTGCCGGGCAAGTCAGGGGATTGGGCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATAATCGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-9 (SEQ ID NO:480)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGGGCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTTTATTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-10 (SEQ ID NO:481)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTACTCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10S

49/93

>DOM4-122-11 (SEQ ID NO:482)

GACATCCAGATGACCCAGTCTCCGTCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGCGATTGGTCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCCATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATAATGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-12 (SEQ ID NO:483)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTGGTCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATGGTTTTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-13 (SEQ ID NO:484)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTACGAAGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCCATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATCATTTCGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-14 (SEQ ID NO:485)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCTATTGGGCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATTATCTTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-15 (SEQ ID NO:486)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCGGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCGTATTGGTGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCCCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATTTTGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-16 (SEQ ID NO:487)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATCATGGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-17 (SEQ ID NO:488)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCGATTTTAAAGGAGTTACGTTGGTACCAGCAGAAACCA
GAGGAAGCCCCCTATGCTCCTGATCCATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGTATCATGGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10T

50/93

>DOM4-122-18 (SEQ ID NO:489)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGAGATTGGGCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACAGTATTTTACGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-19 (SEQ ID NO:490)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCCTATTGGTATTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGTACGTACTACTGTCAACAGTATCATGGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACAG

>DOM4-122-20 (SEQ ID NO:491)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCTATTGGCCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCGAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGTACGTACTACTGTCAACAGTATAATGGTTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-21 (SEQ ID NO:492)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTCTATTGGTCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGTACGTACTACTGTCAACAGTATTATGATTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-22 (SEQ ID NO:493)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCCTATTGGTCGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGTACGTACTACTGTCAACAGTATTCTGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-25 (SEQ ID NO:494)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-26 (SEQ ID NO:495)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10U

51/93

>DOM4-122-27 (SEQ ID NO:496)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-28 (SEQ ID NO:497)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-29 (SEQ ID NO:498)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-30 (SEQ ID NO:499)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCCTGATCTATCATGCGTCCAGGTTGATAAAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-31 (SEQ ID NO:500)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTTCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-32 (SEQ ID NO:501)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCCTGATCTATCATGCGTCCAGGTTGTACAAAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-33 (SEQ ID NO:502)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCCTGATCTATCATGCGTCCAGGTTGCAATCAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10V

52/93

>DOM4-122-34 (SEQ ID NO:503)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTATCATGCGTCCAGGTTGCAATCAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-35 (SEQ ID NO:504)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCTTGATCTATCATGCGTCCAGGTTGATAAAAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-36 (SEQ ID NO:505)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCTTGATCTATCATGCGTCCAGGTTGTACAAAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-37 (SEQ ID NO:506)

GACATCCAGATGATCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTACTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-38 (SEQ ID NO:507)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCGAACGG

>DOM4-122-39 (SEQ ID NO:508)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGGTTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-40 (SEQ ID NO:509)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCCTAAGGTGCTGATCTTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10W

53/93

>DOM4-122-41 (SEQ ID NO:510)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCAGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTACCACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-42 (SEQ ID NO:511)
GGCATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCTCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-43 (SEQ ID NO:512)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCTAAGCTGCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCACTATCAGTAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-44 (SEQ ID NO:513)
GACATCCAGATGACCCAGTTTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCTCC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTAGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACATTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-45 (SEQ ID NO:514)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-46 (SEQ ID NO:515)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAATC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTGCTGATCTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-47 (SEQ ID NO:516)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAATCCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACCTCTCATATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGCTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10X

54/93

>DOM4-122-48 (SEQ ID NO:517)

GACATCCAGATGACCCAGTCTCCACCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTGCCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-49 (SEQ ID NO:518)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-50 (SEQ ID NO:519)

GACATCCAGATGACCCAGTCTCCATCCTCTCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGGCAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
TGGACCAAGGTGGAAATCAAACGG

>DOM4-122-51 (SEQ ID NO:520)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGTTCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACATACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-52 (SEQ ID NO:521)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACAAAGGTGGAAATCAAACGG

>DOM4-122-54 (SEQ ID NO:522)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCCGCTGATCTATCATGCGTCCAGATTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-55 (SEQ ID NO:523)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTGCGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10Y

55/93

>DOM4-122-56 (SEQ ID NO:524)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-57 (SEQ ID NO:525)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCATGTCAACC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGGACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGATGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-58 (SEQ ID NO:526)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTACGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-59 (SEQ ID NO:527)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCAGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGTCAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGCGGAATCAAACGG

>DOM4-122-60 (SEQ ID NO:528)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTGCGCC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-61 (SEQ ID NO:529)
GGCATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGCCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-62 (SEQ ID NO:530)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCCGGACAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGGTGCTGATCTTTTCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

FIG. 10Z

56/93

>DOM4-122-63 (SEQ ID NO:531)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTTTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-64 (SEQ ID NO:532)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GATGATTCTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTCCGGCCAA
GGGACCAGGTGGAATCAAACGG

>DOM4-122-65 (SEQ ID NO:533)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCCATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-66 (SEQ ID NO:534)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTGCTGATCTTTATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTATGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-67 (SEQ ID NO:535)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-68 (SEQ ID NO:536)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCAGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-122-69 (SEQ ID NO:537)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCCGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGATAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCAGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTCCGGCCAA
GGGACCAAGGTGGAATCAAACGG

FIG. 10AA

57/93

>DOM4-122-70 (SEQ ID NO:538)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGCAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCCGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-71 (SEQ ID NO:539)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACGTGCCGGGCAAGTCAGTGGGTTGGTAGGGAGTTACGTTGGTACCAGCAGATAACCA
GGGAAAGCCCCCTAAGCAGCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCGGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-72 (SEQ ID NO:540)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCATGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGGACCAGCAGAAACCA
GGGAAAGCCCCCTAAGTTCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGATGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-122-73 (SEQ ID NO:541)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCAGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTGGATTGGTAGGGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGGGCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGGGTGGCCTCTGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-123 (SEQ ID NO:542)

GACATCCACATGACCCAGTCTCCATCCTCCCTGTCGATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCATATTGGGCGTTCGTTACAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTATACGTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGCAGGGGGAGTTTCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-124 (SEQ ID NO:543)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCGATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCATATTAAGAATTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCATGCGTCCACGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATATGGATGAGCCTCGTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-125 (SEQ ID NO:544)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCGATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGTTATTAGTGTGCTTTAAATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATCAGGGGTCCATTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGAGTTGGCAGTGGCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10BB

58/93

>DOM4-126 (SEQ ID NO:545)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGCTATTGGTAATATGTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATAATGCGTCCTATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTATGCTACGTACTACTGTCAACAGAGGGAGATGATTCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGGAATCAAACGG

>DOM4-127 (SEQ ID NO:546)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTGGTGAGGAGTTACTTTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTTCGGCGTCCTCGTTGCGAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGTGACTTCTCCTAATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-128 (SEQ ID NO:547)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGGGATTCAGACGTTTTTATATTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATTCTAGTTCCATTTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATGGGAATTATCCTTTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129 (SEQ ID NO:548)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCTCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-1 (SEQ ID NO:549)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTTCTGATCTATCATGCGTCCAGGTTGCAACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-2 (SEQ ID NO:550)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCGTCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTTCTGATCTATCATGCGTCCAGGTTGCAACATGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-3 (SEQ ID NO:551)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTGTGTTTCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10CC

59/93

>DOM4-129-4 (SEQ ID NO:552)

GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCCGAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-5 (SEQ ID NO:553)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTATGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-6 (SEQ ID NO:554)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-7 (SEQ ID NO:555)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTATGCCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGAGGATCTGGGACAGATTTCTCTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-8 (SEQ ID NO:556)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGGTTCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGTCTCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTCCGGCCAG
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-9 (SEQ ID NO:557)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAGGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGATCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-10 (SEQ ID NO:558)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCTAGTCAGAATATTGGTTCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10DD

60/93

>DOM4-129-11 (SEQ ID NO:559)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCT
GGGAAAGACCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCAAAGAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACATATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-129-12 (SEQ ID NO:560)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCTAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATTTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-129-13 (SEQ ID NO:561)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGTTCGATTGGTTCGTCGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-129-14 (SEQ ID NO:562)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGCCCCCTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-129-15 (SEQ ID NO:563)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCAAAGTGGAGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-129-16 (SEQ ID NO:564)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-129-17 (SEQ ID NO:565)
GAGATCAAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCTTGATCTATCATGCGTCCAGGTTGCTGAAGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACATACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

FIG. 10EE

61/93

>DOM4-129-18 (SEQ ID NO:566)

CCGATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAGTAGTATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATGAAGGGGTGCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-19 (SEQ ID NO:567)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAATAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATGAAGGGGTGCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-20 (SEQ ID NO:568)

GACATCCAGATGACTCAGTCTCCATCCTCTCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCTACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-21 (SEQ ID NO:569)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCGACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-22 (SEQ ID NO:570)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAGGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGATCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-23 (SEQ ID NO:571)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGACCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCAACGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-24 (SEQ ID NO:572)

AATATCGATATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10FF

62/93

>DOM4-129-25 (SEQ ID NO:573)
CATATCTCTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAGTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATTAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-26 (SEQ ID NO:574)
GAGATCAGGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAATAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAAGGGGGTCCCATCA
CGTTTCAGTGGCGGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-27 (SEQ ID NO:575)
AGGATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAATAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATTAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-28 (SEQ ID NO:576)
CCTATCCGGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTGCTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATTAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-29 (SEQ ID NO:577)
ACGATCTCTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAGTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAGGGGGGCCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-31 (SEQ ID NO:578)
CGTATCCTTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCTTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCATAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-32 (SEQ ID NO:579)
GGGATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTATTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCATAAGGGGGGCCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10GG

63/93

>DOM4-129-33 (SEQ ID NO:580)

AGTATCGTTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCATAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-34 (SEQ ID NO:581)

GATATCCTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTACTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTAGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-35 (SEQ ID NO:582)

CAGATCAATATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAGTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATTAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-37 (SEQ ID NO:583)

ACGATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTGAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATTAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-38 (SEQ ID NO:584)

CAGATCCTTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAGTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATGAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-39 (SEQ ID NO:585)

CAGATCGTTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTGGTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-40 (SEQ ID NO:586)

GATATCTTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTTCTAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGATGAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10HH

64/93

>DOM4-129-41 (SEQ ID NO:587)

GGTATCGAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAATAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGCATAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-42 (SEQ ID NO:588)

GGGATCGTTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAATAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAAGGGAGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-43 (SEQ ID NO:589)

CCGATCAAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTAGGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATGATGGAGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-129-44 (SEQ ID NO:590)

AATATCGTTATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAATATTGATCGTGAGTTACGTTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTATGTTCCCTGATCTATCATGCGTCCAGGTTGTATAAGGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATCATGATTTTCCTCTTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130 (SEQ ID NO:591)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-1 (SEQ ID NO:592)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-2 (SEQ ID NO:593)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 10II

65/93

>DOM4-130-3 (SEQ ID NO:594)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-4 (SEQ ID NO:595)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTTCCACCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-5 (SEQ ID NO:596)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTCCCTGAATTTAGAGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-6 (SEQ ID NO:597)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTGTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-7 (SEQ ID NO:598)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGGAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTTGTACCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-8 (SEQ ID NO:599)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCGGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTTGTACCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-9 (SEQ ID NO:600)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAGGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTACCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 10JJ

66/93

>DOM4-130-10 (SEQ ID NO:601)

GACATCCAGATGACCCAGTCTCCACCTCCCTGTCTGCATCTGTAGGAGACCGGTCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTGACCCGTCTTTTACTTGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-11 (SEQ ID NO:602)

GACATCCAGGTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTACCC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-12 (SEQ ID NO:603)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTACCC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTGGATGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-13 (SEQ ID NO:604)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTACCC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAACCTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACCACCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-14 (SEQ ID NO:605)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTACCC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACTACCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-15 (SEQ ID NO:606)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTACCC
ATCACTTGCCGGGCAAGTCAGGATATTTGGCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGGAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-16 (SEQ ID NO:607)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTACCC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGGAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATCTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 10KK

67/93

>DOM4-130-17 (SEQ ID NO:608)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAGGATTTTGCTACGTACTACTGTCAACCGTCTTTCTTTATCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-18 (SEQ ID NO:609)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTTACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTCTTTATCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-19 (SEQ ID NO:610)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTCTTTATCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-20 (SEQ ID NO:611)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTGGCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTATGTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-21 (SEQ ID NO:612)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTCTTTATCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-22 (SEQ ID NO:613)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAAACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTGTCTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-23 (SEQ ID NO:614)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTGTCTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 10LL

68/93

>DOM4-130-24 (SEQ ID NO:615)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAAATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-25 (SEQ ID NO:616)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAAACTGGTATCAGCAGAAACCA
GAGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTGTACCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-26 (SEQ ID NO:617)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGACAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-27 (SEQ ID NO:618)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTTTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCCATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGCGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGGCGG

>DOM4-130-28 (SEQ ID NO:619)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTATCTGAATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTTTATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-31 (SEQ ID NO:620)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTTCGTCTTATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-32 (SEQ ID NO:621)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCCGTGGTGTTCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 10MM

69/93

>DOM4-130-33 (SEQ ID NO:622)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTCTTTGGCTTCCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-34 (SEQ ID NO:623)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCGGTCTTACTTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-35 (SEQ ID NO:624)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGCTGGAAATCAGACGG

>DOM4-130-36 (SEQ ID NO:625)

GACATCCAGATGACCCAGGCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGACACCA
GGGAATGCCCTAAGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-37 (SEQ ID NO:626)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGTTATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAGGCTCCTGATCTATGGTACGTCCAATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-38 (SEQ ID NO:627)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAGGACGTCGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-39 (SEQ ID NO:628)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCACTGTGGGTTCCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 10NN

70/93

>DOM4-130-40 (SEQ ID NO:629)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCGCTTTGGTTTCCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-41 (SEQ ID NO:630)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCCATCATTGTTCCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-42 (SEQ ID NO:631)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCTCTAAGCTCCTGATCTCGAGTAGTTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-43 (SEQ ID NO:632)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTCTTTGGTTTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-44 (SEQ ID NO:633)

GACATCCAGATGACCCAGTCTCCACCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTCTCTTTCGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-45 (SEQ ID NO:634)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCCTTTATTCGTCCGAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-47 (SEQ ID NO:635)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTCGTGGTCTTCCCTTTTGGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCGGCCAA
GGGACCAAGGTGGAAATCAGACGG

FIG. 1000

71/93

>DOM4-130-48 (SEQ ID NO:636)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-49 (SEQ ID NO:637)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGGTACGTCCGATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-50 (SEQ ID NO:638)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-52 (SEQ ID NO:639)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAGACGG

>DOM4-130-54 (SEQ ID NO:640)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-55 (SEQ ID NO:641)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCTGATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-56 (SEQ ID NO:642)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCGGATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10PP

72/93

>DOM4-130-57 (SEQ ID NO:643)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGCGATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-130-58 (SEQ ID NO:644)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCAGATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-130-59 (SEQ ID NO:645)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGACGATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-130-60 (SEQ ID NO:646)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGAGTATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTACGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-130-61 (SEQ ID NO:647)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGGCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-130-62 (SEQ ID NO:648)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGGGTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

>DOM4-130-63 (SEQ ID NO:649)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTATTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAATCAAACGG

FIG. 10QQ

73/93

>DOM4-130-64 (SEQ ID NO:650)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCTTCTGGGTACTTTTCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-65 (SEQ ID NO:651)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTGCTTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-66 (SEQ ID NO:652)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTCTGTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-67 (SEQ ID NO:653)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACCATCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-68 (SEQ ID NO:654)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACTGGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-69 (SEQ ID NO:655)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTCCTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-70 (SEQ ID NO:656)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10RR

74/93

>DOM4-130-71 (SEQ ID NO:657)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-72 (SEQ ID NO:658)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTACCTGAATTTAATGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-73 (SEQ ID NO:659)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTACCTGAATTTACTGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAGGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-74 (SEQ ID NO:660)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGCAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTACCTGAATTTAATGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-75 (SEQ ID NO:661)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTACCTGAATTTAGCGTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-76 (SEQ ID NO:662)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTACCTGAATTTACTGTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-77 (SEQ ID NO:663)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTTACCTGAATTTAACCCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GATGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10SS

75/93

>DOM4-130-78 (SEQ ID NO:664)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTACCTTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-79 (SEQ ID NO:665)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAAAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-80 (SEQ ID NO:666)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAAAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-81 (SEQ ID NO:667)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGAGTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-82 (SEQ ID NO:668)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGACCAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-83 (SEQ ID NO:669)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGAACAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-84 (SEQ ID NO:670)

GACATCCAGATGACTCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGTACAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10TT

76/93

>DOM4-130-85 (SEQ ID NO:671)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCTCAGTGGAGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-86 (SEQ ID NO:672)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCTCAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-87 (SEQ ID NO:673)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCGGAGTGGCGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-88 (SEQ ID NO:674)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCCAGTGGCGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-89 (SEQ ID NO:675)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCCCCCTGATCAATTTTGGTTCCGAGTTGCAACCCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-90 (SEQ ID NO:676)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAACCCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-91 (SEQ ID NO:677)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGTCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAACACGGCGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10UU

77/93

>DOM4-130-92 (SEQ ID NO:678)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAACTCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-93 (SEQ ID NO:679)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-94 (SEQ ID NO:680)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCTGAGTTGCAATTCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-95 (SEQ ID NO:681)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAACAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-96 (SEQ ID NO:682)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTACCCCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-97 (SEQ ID NO:683)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTAAGCCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-98 (SEQ ID NO:684)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATTAGCAGTCTGCAACCT
GAAGATTTGCTATGTACTACTGTGCGCCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10VV

78/93

>DOM4-130-99 (SEQ ID NO:685)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTTCCTCCGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-100 (SEQ ID NO:686)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCTCCCGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-101 (SEQ ID NO:687)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAAGCGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-102 (SEQ ID NO:688)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCGGTCTGCAACCT
GAAGATTTGCTACGTACTATTGTCAAGCGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-103 (SEQ ID NO:689)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAAGGGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-104 (SEQ ID NO:690)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-105 (SEQ ID NO:691)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCCACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10WW

79/93

>DOM4-130-106 (SEQ ID NO:692)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCATGTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-107 (SEQ ID NO:693)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCGTCTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-108 (SEQ ID NO:694)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAAATTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-109 (SEQ ID NO:695)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTCCTTTGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-110 (SEQ ID NO:696)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTACGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-111 (SEQ ID NO:697)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATAGCGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-112 (SEQ ID NO:698)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATCTCGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10XX

80/93

>DOM4-130-113 (SEQ ID NO:699)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATGGCGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-114 (SEQ ID NO:700)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCCGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTCGGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-115 (SEQ ID NO:701)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATCTGGGTTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-116 (SEQ ID NO:702)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTTTCGTCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-117 (SEQ ID NO:703)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTTCGTCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-118 (SEQ ID NO:704)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGTGTCCGAGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-119 (SEQ ID NO:705)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTTGGTTCAGCTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTCGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10YY

81/93

>DOM4-130-120 (SEQ ID NO:706)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGCGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-121 (SEQ ID NO:707)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCACGTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-122 (SEQ ID NO:708)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGACTTGCAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-123 (SEQ ID NO:709)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCGGAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-124 (SEQ ID NO:710)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTTCTGATCAGCTTTGGTTCCGAGTTGCAACCCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-125 (SEQ ID NO:711)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCGGCCCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-130-126 (SEQ ID NO:712)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCAATTTTGGTTCCGAGTTGCGGCCCGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10ZZ

82/93

>DOM4-130-127 (SEQ ID NO:713)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCAAAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

>DOM4-130-128 (SEQ ID NO:714)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCGGAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

>DOM4-130-129 (SEQ ID NO:715)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCGGAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

>DOM4-130-130 (SEQ ID NO:716)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGACGATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCAAAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGTCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

>DOM4-130-131 (SEQ ID NO:717)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGACGATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAATTTGGTTCCGAGTTGCAAAAGTGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACCGGCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

>DOM4-130-132 (SEQ ID NO:718)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCAAAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGGCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

>DOM4-130-133 (SEQ ID NO:719)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGACGATTTACCTGAATTTAGACTGGTACCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCAGCTTTGGTTCCGAGTTGCAAAAGGGTGTCCCATCA
CGTTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTGCTACGTACTACTGTCAACAGGCTTTTACTTCCCTTATACGTTTCGGCCAA
GGGACCAAAGTGGAATCAAACGG

FIG. 10AAA

83/93

>DOM4-131 (SEQ ID NO:720)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGCAGATTTATAATGCTTTACGGTGGTACCAGCAGAAACCA
GGGAAAGCCCGTAAGCTCCTGATCTATCATAAGTCCCAGTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGACTTATAGTTTTCCTCATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-132 (SEQ ID NO:721)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCAACC
ATCACTTGCCGGGCAAGTCAGGATATTTGGCTTAATTTATCGTGGTATCAGCAGAAACCA
GGGAAAGCCCGTAAGCTCCTGATCTATGATGGTTCCACTTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACCGTCGTTTATTTGGCCTTATACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

>DOM4-133 (SEQ ID NO:722)
GACATCAAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACT
ATCACTTGCCGGGCAAGTCAGAATATTGGTAGGGAGTTACGGTGGTATCAGCAGAAACCA
GGGAAAGCCCGTAAGCTCCTGATCTATCATGCGTCCCATTTGCAAAGTGGGGTCCCATCA
CGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCTACGTACTACTGTCAACAGTATTATTATTTTCCTCTACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGG

FIG. 10BBB

84/93

VKs selected vs MSA

Kabat_Numbering	5	10	15	20	25	30	35
MSA16	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q S I I K H L K W						
MSA 12	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q S I F R H L K W						
MSA 26	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q S I Y Y H L K W						
Kabat_Numbering	40	45	50	55	60	65	70
MSA16	Y Q Q K P G K A P K L L I Y G A S R L Q S G V P S R F S G S G S G T D						
MSA 12	Y Q Q K P G K A P K L L I Y A A S R L Q S G V P S R F S G S G S G T D						
MSA 26	Y Q Q K P G K A P K L L I Y K A S T L Q S G V P S R F S G S G S G T D						
Kabat_Numbering	75	80	85	90	95	100	105
MSA16	F T L T I S S L Q P E D F A T Y Y C Q Q G A R W P Q T F G Q G T K V E						
MSA 12	F T L T I S S L Q P E D F A T Y Y C Q Q V A L Y P K T F G Q G T K V E						
MSA 26	F T L T I S S L Q P E D F A T Y Y C Q Q V R K V P R T F G Q G T K V E						
Kabat_Numbering							
MSA16	I K R						
MSA 12	I K R						
MSA 26	I K R						

FIG. 11A

85/93

VKs selected vs RSA

Kabat_Numbering	5	10	15	20	25	30	35																												
<u>DOM7r-1</u>	D	I	Q	T	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	Y	I	G	R	Y	L	R	W
<u>DOM7r-3</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	Y	I	G	R	Y	L	R	W
<u>DOM7r-4</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	W	I	G	R	Y	L	R	W
<u>DOM7r-5</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	Y	I	S	R	Q	L	R	W
<u>DOM7r-7</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	Y	I	G	R	Y	L	R	W
<u>DOM7r-8</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	W	I	H	R	Q	L	K	W

Kabat_Numbering	40	45	50	55	60	65	70																												
<u>DOM7r-1</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	D	S	S	V	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7r-3</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	D	S	S	V	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7r-4</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	N	G	S	Q	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7r-5</u>	Y	Q	Q	K	P	G	K	A	P	R	L	L	I	Y	G	A	S	V	L	Q	S	G	I	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7r-7</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	D	S	S	V	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7r-8</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	Y	A	S	I	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D

Kabat_Numbering	75	80	85	90	95	100	105																												
<u>DOM7r-1</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	R	Y	R	M	P	Y	T	F	G	Q	G	T	R	V	E
<u>DOM7r-3</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	R	Y	M	Q	P	F	T	F	G	Q	G	T	K	V	E
<u>DOM7r-4</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	R	Y	L	Q	P	Y	T	F	G	Q	G	T	K	V	E
<u>DOM7r-5</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	R	Y	I	T	P	Y	T	F	G	Q	G	T	K	V	E
<u>DOM7r-7</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	R	Y	S	S	P	Y	T	F	G	Q	G	T	K	V	E
<u>DOM7r-8</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	T	F	S	K	P	S	T	F	G	Q	G	T	K	V	E

Kabat_Numbering	
<u>DOM7r-1</u>	I K R
<u>DOM7r-3</u>	I K R
<u>DOM7r-4</u>	I K R
<u>DOM7r-5</u>	V K R
<u>DOM7r-7</u>	I K R
<u>DOM7r-8</u>	I K R

FIG. 11B

86/93

VKs selected vs HSA

Kabat_Numbering	5	10	15	20	25	30	35																												
<u>DOM7h-2</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	K	I	A	T	Y	L	N	W
<u>DOM7h-3</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	W	I	D	T	G	L	A	W
<u>DOM7h-4</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	E	I	Y	S	W	L	A	W
<u>DOM7h-6</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	S	I	S	S	Y	L	N	W
<u>DOM7h-1</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	S	I	S	S	Y	L	N	W
<u>DOM7h-7</u>	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	S	I	S	S	Y	L	N	W

Kabat_Numbering	40	45	50	55	60	65	70																												
<u>DOM7h-2</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	R	S	S	S	L	Q	S	A	V	P	S	R	F	S	G	S	G	S	G	T	V
<u>DOM7h-3</u>	Y	Q	Q	K	P	G	K	A	P	R	L	L	I	Y	N	V	S	R	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7h-4</u>	Y	Q	Q	R	P	G	K	A	P	K	L	L	I	Y	N	A	S	H	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7h-6</u>	Y	Q	Q	K	P	G	K	A	P	T	L	L	I	Y	R	L	S	V	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7h-1</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	R	N	S	F	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
<u>DOM7h-7</u>	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	R	N	S	Q	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D

Kabat_Numbering	75	80	85	90	95	100	105																												
<u>DOM7h-2</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	T	Y	A	V	P	P	T	F	G	Q	G	T	K	V	E
<u>DOM7h-3</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	Y	W	G	S	P	T	T	F	G	Q	G	T	K	V	E
<u>DOM7h-4</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	V	I	G	D	P	V	T	F	G	Q	G	T	K	V	E
<u>DOM7h-6</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	T	Y	N	V	P	P	T	F	G	Q	G	T	K	V	E
<u>DOM7h-1</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	T	Y	T	V	P	P	T	F	G	Q	G	T	K	V	E
<u>DOM7h-7</u>	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	T	F	A	V	P	P	T	F	G	Q	G	T	K	V	E

Kabat_Numbering	
<u>DOM7h-2</u>	I K R
<u>DOM7h-3</u>	I K R
<u>DOM7h-4</u>	I K R
<u>DOM7h-6</u>	I K R
<u>DOM7h-1</u>	I K Q
<u>DOM7h-7</u>	I K R

FIG. 11C

87/93

VHs selected vs HSA

Kabat_Numbering	5	10	15	20	25	30	35
<u>DOM7h-22</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCAASGFTFSKYWM S
<u>DOM7h-23</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCAASGFTFYDYNM S
<u>DOM7h-24</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCAASGFTFHRYSM S
<u>DOM7h-25</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCAASGFTFWKYNM A
<u>DOM7h-26</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCTASGFTFD EYNM S
<u>DOM7h-21</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCAASGFTFD LYDM S
<u>DOM7h-27</u>	EVQL	L	ESGG	G	LVQP	G	GSLRLSCAASGFTFS DYRM S
Consensus	<u>EVQL</u>	<u>L</u>	<u>ESGG</u>	<u>G</u>	<u>LVQP</u>	<u>G</u>	<u>GSLRLSCAASGFTFX XYNM S</u>

Kabat_Numbering	40	45	50	54	59	64	69
<u>DOM7h-22</u>	WVRQ	A	PGKG	L	EWVS	S	IDFMGPHTYYADSVKGRFT I
<u>DOM7h-23</u>	WVRQ	A	PGKG	L	EWVS	T	ITHTGGVTYYADSVKGRFT I
<u>DOM7h-24</u>	WVRQ	A	PGKG	L	EWVS	T	ILPGGDVTYYADSVKGRFT I
<u>DOM7h-25</u>	WVRQ	A	PGKG	L	EWVS	T	ILGEGNNTYYADSVKGRFT I
<u>DOM7h-26</u>	WVRQ	A	PGKG	L	EWVS	T	ILPHGDRTYADSVKGRFT I
<u>DOM7h-21</u>	WVRQ	A	PGKG	L	EWVS	S	IVNSGVRTYYADSVKGRFT I
<u>DOM7h-27</u>	WVRQ	A	PGKG	L	EWVS	T	IISNGKFTYYADSVKGRFT I

Kabat_Numbering	74	79	82b	86	91	96	100a
<u>DOM7h-22</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKGR TSML P
<u>DOM7h-23</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKQ NPSYQ -
<u>DOM7h-24</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKQ TPDYM -
<u>DOM7h-25</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKT M DYK -
<u>DOM7h-26</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKQ DPLYR -
<u>DOM7h-21</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKL N QSYH W
<u>DOM7h-27</u>	SRDN	S	KNTL	Y	LQMN	S	LRAEDTAVYYCAKQ DWMYM -

Kabat_Numbering		100o		105		110	
<u>DOM7h-22</u>	M K G K	F	D Y W G	Q	G T L V	T	V S S
<u>DOM7h-23</u>	- - - -	F	D Y W G	Q	G T L V	T	V S S
<u>DOM7h-24</u>	- - - -	F	D Y W G	Q	G T L V	T	V S S
<u>DOM7h-25</u>	- - - -	F	D Y W G	Q	G T L V	T	V S S
<u>DOM7h-26</u>	- - - -	F	D Y W G	Q	G T L V	T	V S S
<u>DOM7h-21</u>	D - - -	F	D Y W G	Q	G T L V	T	V S S
<u>DOM7h-27</u>	- - - -	F	D Y W G	Q	G T L V	T	V S S

FIG. 11D

88/93

VKs selected vs HSA and RSA

Kabat_Numbering	5	10	15	20	25	30	35
<u>DOM7h-8</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q S I S S Y L N W						
<u>DOM7r-13</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q H I H R E L R W						
<u>DOM7r-14</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q H I H R E L R W						
Kabat_Numbering	40	45	50	55	60	65	70
<u>DOM7h-8</u>	Y Q Q K P G K A P K L L I Y R N S P L Q S G V P S R F S G S G S G T D						
<u>DOM7r-13</u>	Y Q Q K P G K A P K L L I Y Q A S R L Q S G V P S R F S G S G S G T D						
<u>DOM7r-14</u>	Y Q Q K P G K A P K L L I Y Q A S R L Q S G V P S R F S G S G S G T D						
Kabat_Numbering	75	80	85	90	95	100	105
<u>DOM7h-8</u>	F T L T I S S L Q P E D F A T Y Y C Q Q T Y R V P P T F G Q G T K V E						
<u>DOM7r-13</u>	F T L T I S S L Q P E D F A T Y Y C Q Q K Y L P P Y T F G Q G T K V E						
<u>DOM7r-14</u>	F T L T I S S L Q P E D F A T Y Y C Q Q R Y R V P Y T F G Q G T K V E						
Kabat_Numbering							
<u>DOM7h-8</u>	I K R						
<u>DOM7r-13</u>	I K R						
<u>DOM7r-14</u>	I K R						

FIG. 11E

89/93

Kabat_Numbering	5	10	15	20	25	30	35
<u>DOM7r-15</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q S I G R R L K W						
<u>DOM7r-16</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q K I Y K N L R W						
<u>DOM7r-17</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q K I Y N N L R W						
<u>DOM7r-18</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q W I Y K S L G W						
<u>DOM7r-19</u>	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q W I Y R H L R W						
Kabat_Numbering	40	45	50	55	60	65	70
<u>DOM7r-15</u>	Y Q Q K P G A A P R L L I Y R T S W L Q S G V P S R F S G S G S G T D						
<u>DOM7r-16</u>	Y Q Q K P G K A P K L L I Y N S S I L Q S G V P S R F S G S G S G T D						
<u>DOM7r-17</u>	Y Q Q K P G K A P K L L I Y N T S I L Q S G V P S R F S G S G S G T D						
<u>DOM7r-18</u>	Y Q Q K P G K A P K L L I Y Q S S L L Q S G V P S R F S G S G S G T D						
<u>DOM7r-19</u>	Y Q Q K P G K A P K L L I Y D A S R L Q S G V P T R F S G S G S G T D						
Kabat_Numbering	75	80	85	90	95	100	105
<u>DOM7r-15</u>	F T L T I S S L Q P E D F A T Y Y C Q Q T S Q W P H T F G Q G T K V E						
<u>DOM7r-16</u>	F T L T I S S L Q P E D F A T Y Y C Q Q R Y L S P Y T F G Q G T K V E						
<u>DOM7r-17</u>	F T L T I S S L Q P E D F A T Y Y C Q Q R W R A P Y T F G Q G T K V E						
<u>DOM7r-18</u>	F T L T I S S L Q P E D F A T Y Y C Q Q Y H Q M P R T F G Q G T K V E						
<u>DOM7r-19</u>	F T L T I S S L Q P E D F A T Y Y C Q Q T H N P P K T F G Q G T K V E						
Kabat_Numbering							
<u>DOM7r-15</u>	I K R						
<u>DOM7r-16</u>	I K R						
<u>DOM7r-17</u>	I K R						
<u>DOM7r-18</u>	I K R						
<u>DOM7r-19</u>	I K R						

FIG. 12

90/93

Kabat_Numbering	5	10	15	20	25	30	35																												
<u>DOM7r-20</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-21</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-22</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-23</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-24</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-25</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-26</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-27</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	P	Y	T	M	S
<u>DOM7r-28</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	M	A	Y	Q	M	A
<u>DOM7r-29</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	K	D	Y	D	M	T
<u>DOM7r-30</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	H	D	Y	V	M	G
<u>DOM7r-31</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	T	A	S	G	F	T	F	R	H	Y	R	M	G
<u>DOM7r-32</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	M	W	D	K	M	G
<u>DOM7r-33</u>	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	W	A	Y	P	M	S

Kabat_Numbering	40	45	50	54	59	64	69																												
<u>DOM7r-20</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-21</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-22</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-23</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-24</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-25</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-26</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-27</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	S	P	F	G	S	T	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-28</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	T	I	H	Q	T	G	F	S	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-29</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	M	I	S	S	S	G	L	W	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-30</u>	W	A	R	Q	A	P	G	K	G	L	E	W	V	S	L	I	K	P	N	G	S	P	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-31</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	W	I	R	P	D	G	T	F	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-32</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	F	I	G	R	E	G	Y	G	T	Y	Y	A	D	S	V	K	G	R	F	T	I
<u>DOM7r-33</u>	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	S	I	S	S	W	G	T	G	T	Y	Y	A	D	S	V	K	G	R	F	T	I

Kabat_Numbering	74	79	82	86	91	96	100																												
<u>DOM7r-20</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	G	G	K	D	F	-	-
<u>DOM7r-21</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	G	N	L	E	P	F	-
<u>DOM7r-22</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	K	L	S	N	G	F	-
<u>DOM7r-23</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	V	V	K	D	N	T	F
<u>DOM7r-24</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	N	T	G	G	K	Q	F
<u>DOM7r-25</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	K	T	G	P	S	S	F
<u>DOM7r-26</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	R	T	E	N	R	G	V
<u>DOM7r-27</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	S	D	V	L	K	T	G
<u>DOM7r-28</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	V	R	S	M	R	P	Y
<u>DOM7r-29</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	G	F	R	L	F	P	R
<u>DOM7r-30</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	G	R	G	R	F	N	V
<u>DOM7r-31</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	S	Y	M	G	D	R	F
<u>DOM7r-32</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	S	V	A	S	F	-	-
<u>DOM7r-33</u>	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	G	G	Q	G	S	F	-

FIG. 13A

91/93

Kabat_Numbering					10				10				11				
<u>DOM7r-20</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-21</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-22</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-23</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-24</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-25</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-26</u>	S	F	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-27</u>	L	D	G	F	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-28</u>	K	F	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-29</u>	T	F	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-30</u>	L	Q	F	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-31</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-32</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S
<u>DOM7r-33</u>	-	-	-	-	D	Y	W	G	Q	G	T	L	V	T	V	S	S

FIG. 13B

92/93

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1  atttctttat aaaccacaac tctgggcccg caatggcagt ccactgcctt gctgcagtca
61  cagaatggaa atctgcagag gcctccgcag tcacctaatc actctcctcc tcttctgtt
121 ccattcagag acgatctgcc gaccctctgg gagaaaatcc agcaagatgc aagccttcag
181 aatctgggat gttaaccaga agaccttcta tctgaggaac aaccaactag ttgctggata
241 cttgcaagga ccaaagtca atttagaaga aaagatagat gtggtaccca ttgagcctca
301 tgctctgttc ttgggaatcc atggagggaa gatgtgcctg tcctgtgtca agtctgggtga
361 tgagaccaga ctccagctgg aggaggttaa catcactgac ctgagcgaga acagaaagca
421 ggacaagcgc ttcgccttca tccgctcaga cagcggcccc accaccagtt ttgagtctgc
481 cgcctgcccc ggttggttcc tctgcacagc gatggaagct gaccagcccc tcagcctcac
541 caatatgcct gacgaaggcg tcatggtcac caaattctac ttccaggagg acgagtagta
601 ctgcccaggc ctgctgttcc ccattcttgc atggcaagga ctgcagggac tgccagtcctc
661 cctgccccag ggctccccgc tatgggggca ctgaggacca gccattgagg ggtggaccct
721 cagaaggcgt cacaagaacc tggtcacagg actctgcctc ctcttcaact gaccagcctc
781 catgctgcct ccagaatggg ctttctaatg tgtgaatcag agcacagcag ccctgcaca
841 aagcccttcc atgtcgctc tgcattcagg atcaaacccc gaccacctgc ccaacctgct
901 ctctcttgc cactgcctct tctcctca tccaccttc ccatgcctg gatccatcag
961 gccacttgat gacccccaac caagtggctc ccacacctg ttttcaaaaa aagaaaagac
1021 cagtccatga gggaggtttt taagggtttg tggaaaatga aaattaggat ttcattgattt
1081 ttttttttca gtccccgtga aggagagccc ttcatttgga gattatgttc tttcggggag
1141 aggctgagga cttaaaatat tcttgcatth gtgaaatgat ggtgaaagta agtggttagct
1201 tttcccttct ttttcttctt tttttgtgat gtcccaactt gtaaaaaatta aaagttagtg
1261 tactatgtta gcccataat ttttttttct cttttaaacc acttcataa tctggactcc
1321 tctgtccagg cactgctgcc cagcctcaa gctccatctc cactccagat tttttacagc
1381 tgctgcagt actttacctc ctatcagaag tttctcagct cccaaggctc tgagcaaatg
1441 tggtctctgg ggggtcttct ttcctctgct gaaggaataa attgctcctt gacattgtag
1501 agcttctggc acttgagagac ttgtatgaaa gatggctgtg cctctgcctg tctccccccac
1561 cgggctggga gctctgcaga gcaggaaaca tgactcgtat atgtctcagg tcctgcagg
1621 gccaaagcacc tagcctcgct cttggcagg actcagcga tgaatgctgt atatgttggg
1681 tgcaaaagttc cctacttctt gtgacttcag ctctgtttta caataaaatc ttgaaaatgc
1741 ctaaaaaaaaa aaaaaaaaaa

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FIG. 14A

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MEICRGLRSH LITLLLFLFH SETICRPSGR KSSKMQAFRI WDVNQKTFYL
RNNQLVAGYL QGPNVNLEEK IDVVPIEPHA LFLGIHGGKM CLSCVKSGDE
TRLQLEAVNI TDLSENKQD KRFAFIRSDS GPTTSFESAA CPGWFLCTAM
EADQPVSLTN MPDEGVMVTK FYFQEDE

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FIG. 14B

93/93

FIG.15

Sequence	
Anti-mouse serum albumin	
A	QVQLQESGGGLVQPGGSLRLSCEASGFTFSRFGMTWVRQAPGKGVVEWV SGISSLG DSTLYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTAVYYC TIGGSLNPGGQGTQVTVSS
B	QVQLQESGGGLVQPGGSLRLSCAASGFTFRNFGMSWVRQAPGKEPEWV SEISGSGENTYADSVKDRFTISRDNAKSTLYLQMNSLKPEDTAVYYC TIGGSLSRSSQGTQVTVSS
C	QVQLQESGGGLVQPGGSLRLTCTASGFTFSFGMSWVRQAPGKGLEWV SAISSDSG TKNYADSVKGRFTISRDNAKKMLFLQMNSLRPEDTAVYYC VIGRGSPSSQGTQVTVSS
D	QVQLQESGGGLVQPGGSLRLTCTASGFTFRSFGMSWVRQAPGKGLEWV SAISADGSDKRYADSVKGRFTISRDNKGKMLTLDMNSLKPEDTAVYYC VIGRGSPASQGTQVTVSS
E	AVQLVESGGGLVQAGDSLRLSCVVS GTFSSAAMGWFRQAPGKEREFV GAIKWSGTSTYYTDSVKGRFTISRDNVKN TVYLQMN NLKPEDTGVYTC AADRDYRDRMGPMTTTDFRFGQGTQVTVSS
F	QVKLEESGGGLVQTGGSLRLSCAASGRTFSSFAMGWFRQAPGREREFV ASIGSSGITTYADSVKGRFTISRDNAKNTVYLQMN SLKPEDTGLCYC AVNRYGIPYRSGTOYQNWGQGTQVTVSS
G	EVQLEESGGGLVQPGGSLRLSCAASGLTFNDYAMGWYRQAPGKERDMV ATISIGGRTYADSVKGRFTISRDNAKNTVYLQMN SLKPEDTALYYCV AHRQTVVRGPYLLWGQGTQVTVSS
H	QVQLVESGGGLVQAGGSLRLSCAASGRTFSNYAMGWFRQAPGKEREFV AGSGRSNSYNYYSDSVKGRFTISRDNAKNTVYLQMN SLKPEDTAVYYC AASTNLWPRDRNLAYXWGQGTQVTVSS
I	EVQLVESGGGLVQAGDSLRLSCAASGRSLGIYRMGWFRQVPGKEREFV AAISWSGGTTRYLDSVKGRFTISR DSTKNVYLQMN SLKPEDTAVYYC AVDSSGRLYWTLSTSYDYWGQGTQVTVSS
J	QVQLVEFGGLVQAGDSLRLSCAASGRSLGIYKMAWFRQVPGKEREFV AAISWSGGTTRYIDSVKGRFTLSRDNTKNMVYLQMN SLKPDDTAVYYC AVDSSGRLYWTLSTSYDYWGQGTQVTVSS
K	EVQLVESGGGLVQAGGSLRLSCAASGRTFSPTYMGWFRQAPGKEREFV AGVTWGSSTFYGDSVKGRFTASRDSAKNTVTLEMN SLNPEDTAVYYC AAAYGGGLYRDP RSYDYWGRGTQVTVSS
L	AVQLVESGGGLVQAGGSLRLSCAASGFTLDAPPIAWFRQAPGKEREGV SCIRDGTTYADSVKGRFTISSDNANNTVYLQTN SLKPEDTAVYYCAA PSGPATGSSHTFGIYWNLRDDYDNWGQGTQVTVSS
M	EVQLVESGGGLVQAGGSLRLSCAASGFTFDHYTIQWFRQVPGKEREGV SCISSSDGSTYYADSVKGRFTISSDNANTVYLQMN TLEPDDTAVYYC AAGGLLLRVEELQASDYDYWGQGIQVTVSS
N	AVQLVDSGGGLVQPGGSLRLSCTASGFTLDYYAIGWFRQAPGKEREGV ACISNSDGSTYYGDSVKGRFTISRDNAKTTVYLQMN SLKPEDTAVYYC ATADRHYSASHHPFADF AFNSWGQGTQVTVSS
O	EVQLVESGGGLVQAGGSLRLSCAAYGLTFWRAAMAWFRAPGKERELV VARNWGDGSTRYADSVKGRFTISRDNAKNTVYLQMN SLKPEDTAVYYC AAVRTYGSATYDIWGQGTQVTVSS
P	EVQLVESGGGLVQDGGSLRLSCIFSGRTFANYAMGWFRQAPGKEREFV AAINRNGGTTNYADALGRFTISRDNNTAFLQMN SLKPDDTAVYYC AAREWPFSTIPSGWRYWGQGTQVTVSS
Q	DVQLVESGGGWVQPGGSLRLSCAASGPTASSHAIGWFRQAPGKEREFV VGINRGGVTRDYADSVKGRFAVSRDNVKN TVYLQMN RLKPEDSAIYIC AARPEYSFTAMSKGDMDYWGKGTLVTVSS